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EFECTO DE LA SUPRESION CRONICA DEL SISTEMA RENINA-ANGIOTENSINA SOBRE LA EXCRECION URINARIA DE ALBUMINA EN PACIENTES CON HIPERTENSION ARTERIAL

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INTRODUCCION

La enfermedad cardiovascular (CV) es la principal causa de mortalidad a nivel mundial, originando aproximadamente el 30% de todas las muertes (1). El aumento de la presión arterial (PA) es probablemente el factor de riesgo CV más directamente relacionado con esta elevada mortalidad, pero a su vez, el más fácilmente modificable. Datos de estudios de cohortes prospectivos han establecido una relación positiva y lineal entre el riesgo de presentar enfermedad CV y la PA, desde valores tan bajos como 115 mmHg de PA sistólica (2). Refrendando esta afirmación, Lawes y sus colaboradores confirmaron que aproximadamente la mitad de la incidencia global de enfermedad CV en 2001 pudiera ser atribuida a un incremento en las cifras de PA (definido como valores ≥ 115 mmHg de PA sistólica)(1). A nivel mundial, 7.6 millones de muertes prematuras (13.5% del total), el 54% de los ictus y el 47% de los casos de enfermedad coronaria fueron causados por niveles elevados de PA. Aproximadamente la mitad de esta incidencia de morbimortalidad CV ocurrió en población hipertensa, pero el resto de los pacientes presentaban cifras menores de PA (115-139 mmHg de PA sistólica)(1).

La progresión desde unos valores elevados de PA a hipertensión arterial establecida ha sido claramente reflejada en los datos del estudio Framingham (3). Los resultados de este relevante estudio también han demostrado que la prevalencia de morbilidad y mortalidad CV es mayor en individuos con PA normal que en aquellos con PA óptima, y que aumenta más aún en los pacientes con PA normal-alta (4). La PA aumenta progresivamente con la edad, aumentando desde cifras tensionales normales a niveles de prehipertensión, para acabar finalmente avanzado a hipertensión arterial establecida. La progresión gradual de la PA también se observa cuando los pacientes no están tratados o lo son de manera insuficiente, poniendo de manifiesto su efecto sobre el desarrollo de ateroesclerosis y lesión de órgano diana (LOD), y acortando el tiempo hasta la aparición de enfermedad CV establecida o enfermedad renal.

Estudios recientes (5,6) han demostrado que la intervención farmacológica podría ser suficiente para prevenir la progresión de PA normal-alta a hipertensión establecida, pudiendo evitar el consiguiente aumento en el riesgo CV. Sin embargo, aunque las guías de las diferentes Sociedades Científicas (7-9) contemplan el uso de fármacos antihipertensivos en situaciones de PA normal-alta cuando asocian daño orgánico, particularmente los supresores del sistema renina-angiotensina-aldosterona (SRAA), se sigue insistiendo en que son necesarios estudios que confirmen estos hallazgos y que investiguen si dicha intervención precoz es coste-efectiva y previene realmente la aparición de morbilidad y mortalidad CV.

Por otro lado, el efecto del tratamiento antihipertensivo sobre la prevención secundaria de eventos CV y la mortalidad global en sujetos sin diagnóstico de hipertensión fue evaluado en un meta-análisis recientemente publicado (10). Sus resultados pusieron de manifiesto que los fármacos antihipertensivos podrían tener ventajas adicionales añadidas al mero hecho de la reducción de las cifras de PA, observándose un descenso en el riesgo de ictus, insuficiencia cardiaca y mortalidad CV y global. Un hecho llamativo fue que la mortalidad CV y la incidencia de infarto de miocardio no fueron significativamente menores en los pacientes no hipertensos que tomaron medicación antihipertensiva. A pesar de ello, la conclusión de los autores fue que la terapia antihipertensiva es beneficiosa para los pacientes con ECV y valores de PA<140/90 mmHg.

El concepto de "continuum cardiovascular" ha sido desarrollado por Eugene Braunwald y Victor Dzau en las dos últimas décadas (11-13). En el momento actual es más conocido como "continuum cardiorenal", debido a la elevada prevalencia de la asociación de enfermedad CV y renal. Este modelo puede ser dividido en tres estadios fundamentales. En el primer estadio, únicamente son detectados los factores de riesgo CV y no existe evidencia de LOD. En este estadio, el control adecuado de la PA y del resto de los factores de riesgo CV modificables (como el tabaquismo, la diabetes, la dislipemia o el síndrome metabólico) puede prevenir el desarrollo de las diferentes formas de daño orgánico que se asocian con un aumento de la morbimortalidad cardiorenal (14-

16). La prevención primaria y el control estricto de todos los factores de riesgo CV puede retrasar o incluso evitar el desarrollo de eventos CV fatales y no fatales. De hecho, disponemos de datos recientes que afirman que cualquiera de los cuatro marcadores principales de LOD (microalbuminuria, hipertrofia ventricular izquierda, aumento de la velocidad de onda de pulso o engrosamiento de la pared carotídea) pueden predecir la aparición de mortalidad CV independientemente de la estratificación del riesgo CV utilizando la tabla de SCORE (17), constituyendo un argumento a favor sobre la utilidad de la prevención del desarrollo de daño orgánico en la práctica clínica diaria mediante un control estricto de todos los factores de riesgo.

El segundo estadio del continuum cardiorenal se caracteriza por la presencia de uno o más de los distintos indicadores de lesión asintomática de daño orgánico (CUADRO 1). El control de la PA y del resto de factores de riesgo CV pueden facilitar la regresión del daño orgánico. Existen numerosas evidencias de que la regresión de la microalbuminuria (18,19) y de la hipertrofia ventricular izquierda (20,21) tiene como consecuencia una disminución del número de eventos CV. Por el contrario, un aumento en la excreción urinaria de albúmina predice la aparición de eventos y de mortalidad CV (19). Estos datos apoyan la necesidad de seguir la evolución de las diversas formas de LOD en los pacientes hipertensos.

El tercer y último estadio del continuum se caracteriza por la presencia de enfermedad CV establecida o de las fases avanzadas de la enfermedad renal, o de ambos, debido a una progresión de la lesión orgánica y de la ateroesclerosis. Ambas situaciones conducen eventualmente a la aparición de un evento CV o a un aumento en la mortalidad. En esta fase, incluso un abordaje estricto e integral de la hipertensión y del resto de factores de riesgo CV con frecuencia únicamente consigue retrasar la incidencia de nuevos eventos CV o renales.

Por tanto, la identificación de pacientes con un riesgo elevado de desarrollar eventos CV o renales mientras se encuentran en los dos primeros estadios del continuum cardiorenal es de gran importancia dado que la mayoría de dichos eventos ocurren en esas dos primeras fases (22,23). Así, resulta fundamental identificar de manera precoz a los pacientes jóvenes (menores de 50 años) con múltiples factores de riesgo CV y/o con presencia de daño orgánico.

La enfermedad renal crónica (definida como albuminuria y/o una tasa estimada de filtración glomerular menor de 60 ml/min/1.73 m2) está ampliamente reconocida como la complicación más importante y frecuente en la evolución de la diabetes, y junto con la hipertensión, constituyen las dos causas más frecuentes de los estadios finales de la enfermedad renal (24,25). La elevación de la PA contribuye de manera significativa al desarrollo y evolución de los estadio finales de la enfermedad renal. La presencia de enfermedad renal crónica, habitualmente considerada como una forma de daño orgánico, puede ser detectada a lo largo del continuum (12,13). Cuanto más elevado es el riesgo CV, mayor es el grado de asociación con la enfermedad renal crónica. Así, existen datos publicados de que un 35% de la población hipertensa con un riesgo CV asociado alto o muy alto presentan valores de tasa de filtración glomerular <60 ml/min/1.73 m2 (26). La coexistencia de enfermedad renal y ECV se acompaña de un significativo peor pronóstico en determinadas situaciones, como enfermedad coronaria estable, insuficiencia cardiaca, revascularización coronaria o enfermedad arterial periférica.

Asimismo, existen evidencias cada vez más numerosas que inciden en la importancia de una detección precoz del daño renal en la población general debido a la citada relación continua entre la enfermedad renal y la ECV; de hecho, la disfunción renal, incluyendo la proteinuria y la microalbuminuria, está considerada en la actualidad como un excelente predictor de desarrollo de complicaciones renales y CV, tanto de eventos como de mortalidad, reforzando la idea sobre la necesidad de una consideración global del daño y del abordaje terapéutico conjunto de la enfermedad renal y de la CV (27-30).

La necesidad de un control estricto de la PA fue puesto de manifiesto por primera vez hace dos décadas en un meta-análisis de todos los estudios disponibles donde los distintos fármacos antihipertensivos (principalmente diuréticos y betabloqueantes) fueron comparados con placebo (31). La aparición de los inhibidores de la enzima convertidora de angiotensina (IECA) y, años más tarde, de los antagonistas de los receptores de angiotensina II (ARA)(32) demostraron que sus efectos consistían, no sólo en conseguir una reducción de

los valores de PA similar a la del resto de los fármacos antihipertensivos, si no que además demostraron tener capacidad para proteger los sistemas CV y renal más allá del beneficio obtenido por el mero descenso de las cifras de PA. Estas ventajas fueron inicialmente demostradas en pacientes con insuficiencia cardiaca y post-infarto de miocardio, pero también en sujetos con enfermedad renal crónica (particularmente en situaciones de nefropatía diabética con proteinuria, tanto micro como macroalbuminuria)(32).

En este aspecto, cualquier terapia antihipertensiva es capaz, a priori, de reducir la albuminuria de forma paralela a la reducción de la PA. Sin embargo, un amplio número de estudios clínicos (BENEDICT, IRMA-2, ROADMAP)(33-35) han demostrado que los IECA y los ARA parecen mostrar una capacidad superior a la hora de reducir la excreción urinaria de albúmina en los pacientes hipertensos en comparación con el resto de tratamientos antihipertensivos, como los antagonistas del calcio, los diuréticos o los betabloqueantes. En esta población, el tratamiento con fármacos que bloqueen el eje renina-angiotensina ha logrado una reducción significativa de la progresión del daño renal y fundamentalmente ha retrasado el desarrollo hacia los estadios avanzados de enfermedad renal crónica en comparación con la terapia convencional. Estas afirmaciones pueden estar en relación con el importante papel que desempeña la angiotensina II en la etiopatogenia de la albuminuria en la diabetes y la hipertensión.

El éxito de los IECA y los ARA a la hora de prevenir y retrasar el desarrollo de daño orgánico (particularmente albuminuria e hipertrofia ventricular izquierda), junto con sus demostrados beneficios una vez que la enfermedad CV está establecida, han aumentado las indicaciones de uso de los supresores del SRAA a los estadios iniciales del continuum cardiorenal, particularmente en aquellos pacientes que presentan un riesgo añadido elevado debido a la sumación de tres o más factores de riesgo CV, la presencia de síndrome metabólico y diabetes o el descubrimiento de lesión precoz de órgano diana (7). Como consecuencia, los bloqueantes del SRAA son considerados como el tratamiento de elección en el manejo de los pacientes hipertensos de alto riesgo CV con o sin diabetes, y se han convertido en la forma más utilizada de tratamiento farmacológico, tanto en monoterapia como en combinación, en la población hipertensa, habiendo

contribuido a mejorar la calidad y la duración de la vida de los pacientes hipertensos con un elevado riesgo CV global (36).

Sin embargo, en los últimos años han aparecido datos que sugieren que la enfermedad CV puede progresar a pesar de un bloqueo prolongado del SRAA (37), pudiendo ser inefectiva e incompleta en determinadas situaciones y grupos de pacientes. Una inhibición incompleta del SRAA puede ser responsable de un daño orgánico residual y de un porcentaje de eventos en pacientes con hipertensión, diabetes, enfermedad renal crónica e insuficiencia cardiaca tratados con IECA o ARA. Así, el bloqueo del SRAA no sería capaz de mantener su capacidad protectora sobre el desarrollo y evolución natural de los distintos marcadores que predicen el desarrollo de enfermedad cardiorenal, como la microalbuminuria (38,39). Este hecho tendría lugar fundamentalmente en pacientes diabéticos y en hipertensos con alto riesgo que hayan desarrollado enfermedad CV. Por tanto, la progresión de los predictores tanto de enfermedad CV como renal bajo una supresión crónica del SRAA debe ser examinada.

Se han encontrado diversas explicaciones para intentar clarificar el por qué de esta progresión de la enfermedad cardiorenal a pesar de la supresión crónica del SRAA.

En primer lugar, sigue siendo desconocido con exactitud el porcentaje de pacientes no respondedores al bloqueo del SRAA, habiéndose publicado diversos estudios donde un número significativo de sujetos desarrollaron microalbuminuria de novo mientras estaban siendo tratados con IECA o ARA a dosis óptimas (ROADMAP, BENEDICT)(35,33). Por otro lado, el bloqueo del SRAA con un solo agente en una localización concreta de la cascada del eje renina-angiotensina puede no ser suficiente para prevenir la evolución del daño orgánico, y tanto la angiotensina como la aldosterona pueden aumentar a niveles similares a los existentes previamente al tratamiento, o incluso incrementarse en algunos pacientes, constituyendo el denominado fenómeno de escape, situación observada en aproximadamente el 30-40% de los pacientes tratados bien con IECA o bien con ARA (37). Este hecho limita la capacidad supresora del SRAA y reduce los beneficios que ambos grupos de fármacos antihipertensivos tienen a

la hora de retrasar la progresión de la enfermedad CV y renal. Finalmente, es probable que la utilización de supresores del SRAA a las dosis máximas recomendadas para el tratamiento de la hipertensión sea insuficiente para lograr un bloqueo completo del SRAA, imposibilitando alcanzar el objetivo de retrasar el desarrollo de enfermedad renal.

Existen numerosas evidencias en los últimos años que han conseguido demostrar que el bloqueo intensivo del SRAA consigue mejorar los resultados cardiorenales. Por un lado, ciertos estudios han sugerido que las dosis suprafisiológicas de un único agente son mucho más efectivas para reducir la proteinuria (40,41). Por otro lado, el concepto del bloqueo dual (asociación de IECA y ARA) fue originalmente considerado como una manera de alcanzar un bloqueo más potente del SRAA que podría mejorar los resultados CV más allá de la reducción de la PA. El tratamiento combinado de ambos grupos terapéuticos se ha convertido en una opción eficaz para evitar el desarrollo de enfermedad renal crónica en pacientes con proteinuria, así como para retrasar la evolución hacia proteinuria en pacientes microalbuminúricos, siendo igualmente efectiva en situaciones de insuficiencia cardiaca congestiva con supresión neurohormonal incompleta (pacientes en los que no es posible asociar betabloqueantes o intolerantes a dosis óptimas de IECA)(42). Sin embargo, disponemos de resultados de estudios recientes que revelan que la supresión agresiva del SRAA mediante el bloqueo dual puede producir efectos deletéreos. Los resultados de un meta-análisis publicado en 2007 demostraron que en los pacientes tratados con IECA y ARA en combinación se observaba una reducción en la tasa de filtrado glomerular estimada y una tendencia al aumento de las cifras de creatinina plasmática, a pesar de una disminución de la proteinuria (43). Estos datos fueron muy similares a los resultados obtenidos del estudio ONTARGET (44), donde el bloqueo dual no ofreció beneficios en pacientes con alto riesgo CV cuando se comparó con cualquiera de los agentes en monoterapia, observándose además un aumento en la aparición de eventos adversos. Asimismo, el control de la PA con este tipo de bloqueo dual ha demostrado ser inferior cuando se compara con el obtenido tanto por IECA como por ARA utilizados en combinación con un diurético o un betabloqueante.

La inhibición de la actividad de la renina plasmática ofrece una reciente alternativa terapeútica eficaz para limitar el primer paso de la cascada del eje renina-angiotensina. Aliskiren, un inhibidor directo de renina de administración oral, ha demostrado ser efectivo, no sólo para controlar la PA en monoterapia y en combinación con diuréticos o calcioantagonistas en los diferentes estadios de la hipertensión en pacientes obesos o con síndrome metabólico (45), si no que además retrasa la progresión hacia albuminuria e hipertrofia ventricular izquierda cuando se añade en pacientes previamente tratados con dosis óptimas de ARA (ALLAY, AVOID)(46,47). Sin embargo, recientemente han aparecido datos contradictorios sobre esta molécula. El estudio ALTITUDE (48) fue diseñado para evaluar los efectos de la combinación de aliskiren con IECA o ARA versus IECA o ARA en monoterapia en pacientes diabéticos tipo 2 con niveles elevados de excreción urinaria de albúmina y tasa de filtrado glomerular 30-60 ml/min/1.73 m2 o historia de enfermedad CV. Hace pocos meses ha sido concluido de manera precipitada siguiendo el consejo del comité regulador debido a un aumento en la incidencia de ictus no fatal, complicaciones renales e hiperkaliemia en el grupo tratado con aliskiren, que han sido atribuidas al control excesivo de la PA y al deterioro de la función renal originado por una mayor supresión del SRAA en pacientes con antecedentes de enfermedad CV y buen control tensional.

La asociación tanto de IECA como de ARA con los bloqueantes de los receptores aldosterónicos (espironolactona y/o eplerenona) está ampliamente aceptada como una importante arma terapeútica en el manejo de los pacientes con insuficiencia cardiaca. El estudio RALES (49) demostró que el tratamiento con espironolactona reducía de manera significativa la morbilidad y la mortalidad en los pacientes con insuficiencia cardiaca y disfunción ventricular severa. En el estudio EPHESUS (50), la terapia con eplerenona obtuvo reducciones importantes en la morbimortalidad asociada a la presencia de fallo cardiaco por disfunción de ventrículo izquierdo tras infarto de miocardio al comparalo con placebo. Se han observado efectos positivos similares al añadir espironolactona

tanto a IECA como a ARA para reducir la proteinuria y prevenir la progresión de la enfermedad renal crónica (51).

Por último, existen formas de hipertensión que también se podrían beneficiar de la supresión intensiva del SRAA. La hipertensión refractaria (HR) se define como la PA que permanece por encima de los objetivos (>140/90 mmHg) a pesar de la utilización simultánea de 3 ó mas fármacos antihipertensivos, uno de ellos un diurético, y todos prescritos a dosis óptimas (52). Su relevancia se explica por el hecho de que amplifica el peor de los pronósticos de cualquiera de los grados de hipertensión. Su prevalencia exacta es desconocida, aunque algunos estudios prospectivos la cifran en un 12-15% de los pacientes hipertensos (53). Sin embargo, datos recientes del registro CARDIORISC revelan que un elevado porcentaje (37.5%) de los pacientes clasificados como hipertensos refractarios realmente presentan fenómeno de bata blanca tras realizar el control tensional mediante la monitorización ambulatoria de PA en 24 horas (MAPA)(54). Asimismo, la resistencia al tratamiento antihipertensivo se asocia con un peor perfil de riesgo CV que el de los pacientes hipertensos bien controlados, incluyendo una mayor reducción de función renal, mayores valores de albuminuria y mayor número de eventos CV (55).

El tratamiento de la HR (52) está dirigido a la identificación y modificación de los hábitos de vida que contribuyen a la resistencia al tratamiento, a la evaluación de las posibles causas secundarias de hipertensión y, fundamentalmente, a la utilización de regímenes efectivos de combinaciones de distintos fármacos.

Las recomendaciones específicas sobre esquemas de tratamiento farmacológico, basados habitualmente en la práctica clínica, incluyen la intensificación del tratamiento diurético (principalmente con agentes de duración prolongada) o bloqueantes de los receptores mineralocorticoideos (56-58). De todas estas opciones terapéuticas, la adición de espironolactona sobre el esquema previo de tratamiento (el cual habitualmente incluye otros supresores del SRAA) ha demostrado ser una herramienta útil para el control de la PA en pacientes con HR verdadera, consiguiendo la reducción de las cifras de PA hasta valores dentro de objetivos en aproximadamente un 50% de los pacientes según algunos estudios recientes (56). Esta importante respuesta favorable puede ser explicada

por la presencia de un aldosteronismo primario no diagnosticado, cuya prevalencia ha sido estimada en un 14-23% (59), que favorecería un remodelado vascular alterado, promoviendo así la resistencia al tratamiento farmacológico. En cualquier caso y a pesar de lo referido con anterioridad, existe un grupo de pacientes hipertensos refractarios que no responden al tratamiento con bloqueantes aldosterónicos.

En conclusión, disponemos de numerosas evidencias que apoyan la utilización de supresores del SRAA en todos los estadios del continuum CV, tanto por su eficacia antihipertensiva como por sus efectos protectores sobre la progresión de la enfermedad cardiorrenal. Sin embargo, datos publicados en los últimos años demuestran cómo el daño orgánico progresa y los eventos CV se siguen produciendo en pacientes tratados con dosis adecuadas de supresores del sistema renina-angiotensina, incluso en aquellos sometidos a bloqueo intensivo del sistema, que asimismo han mostrado evidencias contradictorias en lo referente a su perfil de eventos adversos. Por tanto, son necesarios estudios futuros que confirmen cual es la mejor y más segura forma de mejorar la supresión del SRAA y, en general, una revisión de las implicaciones terapéuticas de la supresión del SRAA con el objetivo de lograr un mejor control de la PA y una mayor reducción en el número de eventos CV

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OBJETIVOS DE LA TESIS

OBJETIVOS DEL TRABAJO 1: "PROGRESION DE LA MICROALBUMINURIA BAJO LA SUPRESION CRONICA DEL SISTEMA RENINA-ANGIOTENSINA-ALDOSTERONA"

OBJETIVOS PRINCIPALES

- Analizar la prevalencia de albuminuria en pacientes con hipertensión arterial esencial remitidos a una Unidad de Hipertensión.
- Analizar la evolución a largo plazo de la albuminuria en una cohorte de pacientes hipertensos tratados con supresión del sistema renina-angiotensina.

OBJETIVOS SECUNDARIOS

- Analizar el grado de control de la presión arterial en los pacientes hipertensos esenciales con excreción urinaria de albúmina elevada.
- Analizar la influencia del grado de control de la presión arterial sobre la evolución de la albuminuria.
- Investigar la asociación de la evolución de la albuminuria con la aparición de eventos cardiovasculares
- Describir otros posibles factores asociados a la progresión de albuminuria en los pacientes hipertensos esenciales.

OBJETIVOS DEL TRABAJO 2: "REVISION DE LOS OBJETIVOS RENALES, CARDIOVASCULARES Y DE MORTALIDAD EN ESTUDIOS CON ANTIHIPERTENSIVOS EN PACIENTES DIABETICOS"

OBJETIVOS PRINCIPALES

- Analizar si los beneficios en términos de mortalidad y morbilidad en pacientes diabéticos dependen exclusivamente de los niveles de presión arterial alcanzados con el tratamiento
- Valorar los posibles efectos adversos metabólicos de algunas familias de fármacos antihipertensivos.

OBJETIVOS SECUNDARIOS

- Investigar la relación entre objetivos secundarios, especialmente renales, y objetivos primarios, particularmente mortalidad CV y global;
- Evaluar las dificultades que el uso de la combinación de dos o más fármacos pueden ocasionar en el diseño e interpretación de los estudios clínicos.

OBJETIVOS DEL TRABAJO 3: "VALIDACION DE UN ESQUEMA TERAPEUTICO PARA EL TRATAMIENTO DE LA HIPERTENSION REFRACTARIA"

OBJETIVOS PRINCIPALES

- Evaluar el resultado de la utilización de nuevas formas de bloqueo del sistema renina-angiotensina (espironolactona y aliskiren) en pacientes con hipertensión refractaria.

OBJETIVOS SECUNDARIOS

- Investigar la seguridad del tratamiento con un bloqueo más completo del sistema renina-angiotensina .

TRABAJO 1º: "PROGRESION DE LA MICROALBUMINURIA BAJO LA SUPRESION CRONICA DEL SISTEMA RENINA-ANGIOTENSINA-ALDOSTERONA"

INTRODUCCION

La microalbuminuria es un predictor del desarrollo de complicaciones renales y cardiovasculares (CV) en pacientes con y sin diagnóstico de diabetes (1,2). Por consiguiente, la detección precoz de microalbuminuria está recomendada por las Guías de las diferentes Sociedades Científicas (3,4). Desde la descripción inicial en los años 80 de la potencialidad del captopril sobre la disminución de la cantidad de proteínas excretadas en la orina (5), la capacidad de la supresión del sistema renina-angiotensina-aldosterona (SRAA) para reducir la albuminuria ha sido ampliamente demostrada tanto en micro como en macroalbuminuria. De hecho, está ampliamente establecido que el bloqueo del SRAA es necesario en pacientes con cantidades aumentadas de albúmina en la orina con el doble objetivo de facilitar el control de la presión arterial (PA) a la vez que se disminuye la cantidad de albúmina en orina, más allá de lo previsto por la mera caída de la PA (3,4,6). Dicho efecto ha demostrado que protege la función renal y retrasa el desarrollo de los estadios finales de la enfermedad renal, particularmente en pacientes con macroalbuminuria (7,8).

Simultáneamente, el papel protector de la supresión del SRAA sobre la enfermedad CV establecida fue demostrado en pacientes con insuficiencia cardiaca (9), post-infarto de miocardio (10) y en sujetos con riesgo CV global elevado (11). Dicha protección podría ser particularmente importante en aquellos pacientes que conjuntamente presentan enfermedad CV establecida e insuficiencia renal crónica (12,13).

Todos estos hallazgos, junto con la bien documentada eficacia antihipertensiva de los supresores del SRAA (3,4), han conducido a la amplia utilización de los inhibidores de la enzima convertidora de angiotensina (IECA) y de los antagonistas de los receptores de angiotensina (ARA), particularmente en los estadios precoces del continuum cardiorenal, cuando únicamente se detectan

factores de riesgo CV y cifras elevadas de PA, aún en ausencia de lesión de órgano diana asintomática.

Sin embargo, datos recientes han sugerido la posibilidad de que la enfermedad cardiorrenal pueda desarrollarse incluso bajo la supresión crónica del SRAA (14), y la evolución de los factores predictores de la enfermedad CV como la microalbuminuria debe ser investigada en pacientes que siguen tratamiento crónico con bloqueantes del SRAA.

En este artículo se realiza una revisión retrospectiva de nuestra experiencia sobre la evolución de la albuminuria en pacientes hipertensos crónicamente tratados (más de 5 años) con supresores del SRAA.

METODOS

Hemos revisado la evolución de 1433 pacientes (media de edad 60.5±12.4 años, 5.3% hombres, 6.6% con diagnóstico de diabetes tipo 2) que acudieron a nuestra Unidad de Hipertensión hospitalaria previamente tratados durante al menos 2 años tanto con IECA como con ARA, a dosis adecuadas, en monoterapia o en combinación con otros agentes antihipertensivos. Nuestro protocolo incluye un estudio basal seguido de un periodo de 3 meses durante el cual se intenta el mejor control posible de los factores de riesgo CV. Con el propósito de este estudio basal, los datos son aquellos obtenidos al final de este periodo de 3 meses de estabilización de los valores. La presencia de formas secundarias de hipertensión arterial fueron excluida. Con posterioridad, los pacientes fueron seguidos durante un periodo mínimo de tres años, con visitas de revisión a nuestra Unidad al menos cada seis meses. Al finalizar este periodo, un grupo de 1141 pacientes eran normoalbuminúricos mientras que los restantes 392 (27.3%) presentaron albuminuria, bien micro (94%) o macro (6%). Ambas formas de albuminuria fueron más prevalentes en pacientes diabéticos que en no diabéticos.

Este artículo contiene un análisis retrospectivo de la excreción urinaria de albúmina en los 1141 pacientes que se mostraron normoalbuminúricos al inicio del estudio y que mantuvieron tratamiento supresor del SRAA a dosis óptimas durante todo el periodo de seguimiento.

Para este estudio retrospectivo definimos “evento albuminuria” tanto como: 1) microalbuminuria de reciente comienzo (cociente albúmina/creatinina 20-200 mg/24 horas en hombres y 30-300 mg/24 horas en mujeres) confirmada al menos en una segunda determinación a lo largo de las determinaciones semestrales realizadas en tres muestras de orina recogida a primera hora de la mañana y 2) cuando la última medición estaba en rango de macroalbuminuria. La presión arterial fue evaluada utilizando un dispositivo validado OMRON semiautomático, medida en condiciones uniformes, y los valores representan la media de tres determinaciones consecutivas.

Los pacientes recibieron durante el seguimiento la dosis más elevada posible de IECA o ARA, acompañado de un diurético o calcioantagonista cuando fue necesario, y la combinación de los tres si la PA se mantenía en valores superiores a 140/90 mmHg.

ANALISIS ESTADISTICO

Las variables cuantitativas fueron representadas como la media ± desviación estándar dado que todas ellas presentaron una distribución normal excepto la albuminuria (mediana y rango interquartílico). Número y porcentaje fueron utilizados para las variables categóricas. Los modelos lineales de repetición generalizada se utilizaron para examinar la evolución cuantitativa de las variables a lo largo del tiempo. El test de Friedman de las medidas repetidas se usó para observar la evolución de la albuminuria a lo largo del periodo de estudio. La evolución de los grupos de albuminuria (en porcentajes) a lo largo del tiempo se estudió mediante el test de la chi-cuadrado para la tendencia. La función de supervivencia de Kaplan-Meier fue utilizada para estudiar el tiempo hasta la aparición del primer evento de microalbuminuria de novo, comparando los distintos grupos de acuerdo a la presencia de eventos CV mediante el test de log-rank.

Por ultimo, el análisis de regresión de Cox se utilizó para identificar las variables asociadas con el tiempo de aparición de microalbuminuria de novo. Las variables independientes consideradas fueron: sexo, edad (años), diabetes (sí, no), aclaramiento de creatinina, albúmina sérica, calcio, índice de Cockroft, MDRD,

colesterol sérico total, HDL-c, LDL-c, creatinina, glucemia, hemoglobina, hematocrito, potasio, sodio, triglicéridos, ácido úrico, número de fármacos antihipertensivos, PA sistólica (PAS), PA diastólica (PAD), grado de control de la hipertensión (<140/90 vs ≥140/90 mmHg), presencia de al menos un evento CV previo (enfermedad coronaria, ictus o enfermedad arterial periférica), aparición de eventos CV durante el periodo de seguimiento (presencia, ausencia) y grupos de albuminuria en el momento basal (normal, normal-alta). Todas las variables que resultaron estadísticamente significativas ($p<0.01$) en los análisis univariantes fueron introducidas en un modelo multivariante de tipo stepwise forward. La significación estadística fue establecida para un valor de $p<0.05$. Fue utilizada la versión 17.0 de SPPS (SPSS Chicago IL, USA) para todos los análisis estadísticos.

RESULTADOS

La tabla 1 contiene los valores basales y la evolución anual de las variables analíticas medidas, así como las cifras de PA y de aclaramiento de creatinina de los 1141 pacientes con normoalbuminuria en el momento basal. La presión arterial permaneció estable durante el periodo de seguimiento, con un 54-56% de los pacientes consiguiendo un control tensional adecuado. Se observó una caída significativa del colesterol total y LDL-c, mientras que el valor de la creatinina plasmática permaneció estable en ausencia de modificaciones en los valores de aclaramiento de creatinina. Un 17.4% del total de los pacientes podrían ser diagnosticados de enfermedad renal crónica (ERC) de acuerdo a los valores de aclaramiento de creatinina (<60 ml/min/1.73 m2). Este porcentaje fue del 16.8% al finalizar el periodo de seguimiento (p NS). La presencia de micro o macroalbuminuria se asoció a un porcentaje significativamente superior de pacientes con ERC, determinado por una reducción en los valores de aclaramiento de creatinina ($p<0.01$ vs microalbuminuria), 27.4% y 42.9% en el momento basal, y 25.3% y 56.9% al final del seguimiento, respectivamente (p NS vs momento basal).

Todos los pacientes recibieron IECA (47%) o ARA (53%) durante el periodo de seguimiento, combinados con un segundo fármaco en un 33.8% de los sujetos

(62% diurético y 30% calcioantagonista) y recibiendo una asociación de tres o más drogas en un 42.6% de los casos. Ningún paciente recibió bloqueantes aldosterónicos durante el seguimiento.

La tabla 2 muestra el aumento de la albuminuria durante el periodo de seguimiento en los 1141 pacientes normoalbuminúricos. Un total de 184 pacientes (16.1%) desarrollaron microalbuminuria de novo mientras que en 11 pacientes (1%) se detectó macroalbuminuria al final del seguimiento (tabla 2). También observamos que la probabilidad de no haber desarrollado "evento albuminuria" fue decreciendo durante los tres años de seguimiento. Particularmente, esta probabilidad fue 0.918 a los 6 meses, 0.911 al primer año, 0.892 al segundo año y 0.890 al tercer año.

Un hecho llamativo fue que el aumento de la microalbuminuria a lo largo de los tres años de seguimiento ocurrió fundamentalmente en el primer año. Este hallazgo puede ser debido a que 171 de los 1141 (15%) pacientes normoalbuminúricos en el momento basal se encontraban en rango de albuminuria normal-alta (10-15 mg/día en varones y 20-30 mg/día en mujeres), valores muy cercanos al rango de microalbuminuria.

De estos 1141 pacientes, un total de 180 (15.8%) presentaban enfermedad CV en el momento de inicio, caracterizada por 205 eventos no-fatales (92 infartos de miocardio, 89 ictus, 24 hospitalizaciones por insuficiencia cardiaca). Durante el seguimiento, un total de 53 pacientes (4.6%) desarrollaron un evento CV (30 infartos de miocardio, 23 ictus y 6 ingresos por insuficiencia cardiaca). La figura 1 muestra que la probabilidad de desarrollar "evento albuminuria" de reciente aparición de acuerdo a la presencia o ausencia de un evento CV previo a su llegada a la Unidad fue significativamente superior en aquellos que presentaban evento CV previo. La microalbuminuria de novo apareció en un 9.9% de los pacientes sin evento previo y en un 17.2% (p=0.003) con evento CV previo a su llegada. Del mismo modo, durante el seguimiento la aparición de microalbuminuria de novo fue observada más frecuentemente en aquellos pacientes que presentaron nuevos eventos CV (18.9% vs 10.7%, p =0.057).

La tabla 3 representa el porcentaje de pacientes con valores de PA controlados por debajo de 140 y/o 90 mmhg durante el seguimiento. Como se puede ver, el mejor control corresponde a aquellos pacientes que permanecieron

normoalbuminúricos durante los tres años. Los individuos que presentaban microalbuminuria en el momento basal y aquellos que la desarrollaron durante el seguimiento, presentaron un control significativamente peor de la PA durante las visitas anuales. El número de fármacos antihipertensivos necesarios para el control fue significativamente mayor en los pacientes con microalbuminuria en situación basal o que la desarrollaron durante el seguimiento. Sin embargo, como se puede ver en la tabla 4, el desarrollo de albuminuria ocurrió con cualquier cifra de PA sistólica mantenido durante el seguimiento, desde valores por debajo de 130 mmHg hasta por encima de 160 mmHg.

Por último, el análisis de regresión múltiple reveló que los factores relacionados con el desarrollo de microalbuminuria fueron: glucosa plasmática (HR 1.014; CI 1.007-1.021, p<0.001), creatinina sérica (HR 2.293; IC 1.366-3.850, p=0.002), número de fármacos antihipertensivos (HR 1.306; IC 1.056-1.613, p=0.014) y los valores iniciales de albuminuria (normal vs normal-alta) (HR 3.145; IC 1.886-5.247, p<0.001).

DISCUSION

Los datos presentados muestran cómo los pacientes que se encontraban bajo supresión crónica del SRAA cuando llegaron a nuestra Unidad tenían una elevada prevalencia de albuminuria. Este porcentaje aumentó durante el seguimiento en condiciones adecuadas de tratamiento. De hecho, la microalbuminuria de novo apareció en un 16.1% de los pacientes normoalbuminúricos, mientras que el 1% desarrolló macroalbuminuria durante los tres años de seguimiento en nuestra Unidad. La prevalencia de microalbuminuria al final del periodo de seguimiento fue superior (43.4%) que la evidenciada en el estudio ACCORD (15), en el cual todos los pacientes eran diabéticos tipo 2 y la mayoría de ellos seguían tratamiento durante años bien con IECA o con ARA. El incremento progresivo en la cantidad de albúmina excretada en la orina en muchos de estos pacientes recuerda los datos del estudio ONTARGET (16), en el cual la albuminuria también aumentó de manera continua durante el periodo de seguimiento. Un hecho relevante del estudio ONTARGET es que aproximadamente dos tercios de los pacientes se encontraban previamente en tratamiento crónico con supresores

del SRAA, en concreto con IECA. Estos datos contrastan con los resultados obtenidos en estudios previos, como el LIFE (17) y el DETAIL (18), en los cuales el descenso inicial en la excreción de albúmina habitualmente se mantuvo durante los primeros años de tratamiento, aunque en el estudio DETAIL la cantidad de albúmina regresó a niveles similares a los de la situación basal después de 5 años de tratamiento (18).

Los pacientes que ya presentaban microalbuminuria a su llegada a nuestra Unidad podrían corresponder al porcentaje de sujetos que no responden a la supresión del SRAA. Dos buenos ejemplos de individuos no respondedores a este tipo de terapia fueron descritos en los estudios BENEDICT (19) y ROADMAP (20), en los cuales un número significativo de pacientes naïve desarrollaron microalbuminuria de novo mientras estaban siendo tratados con IECA y ARA en dosis adecuadas. Existen pocas referencias acerca de estos pacientes no respondedores y menos aún sobre qué hacer con ellos en lo concerniente al tratamiento. Si la prevención de microalbuminuria es importante, éste sería un campo de enorme interés para profundizar en futuros estudios.

Clásicamente se ha reconocido que la progresión de normo a microalbuminuria ocurre aproximadamente en un 2% de los pacientes diabéticos por año (21). Tanto el BENEDICT (19) como el ROADMAP (20) demostraron que este porcentaje puede ser mayor incluso en presencia de supresión del SRAA y, más aún como en el caso del ROADMAP, en situaciones de excelente control tensional (20). Nuestros datos, con un porcentaje minoritario de diabéticos, han evidenciado que este porcentaje alcanza el 16.1% después de tres años de seguimiento y que la aparición de microalbuminuria de novo es particularmente elevada en aquellos pacientes que presentan enfermedad CV establecida (18.9% vs 10.7%). Nuestros datos también demuestran cómo un excelente control tensional en consulta a largo plazo no excluye el desarrollo de microalbuminuria de novo. Nuestros resultados, por tanto, reflejan que el desarrollo de microalbuminuria podría ser particularmente prevalente en pacientes hipertensos de alto riesgo con enfermedad CV establecida en los cuales la enfermedad progresa más rápidamente de lo esperado en presencia de una "adecuada" supresión del SRAA.

De acuerdo con datos anteriores (22), los análisis de regresión múltiple revelan que los factores que promueven el desarrollo de microalbuminuria de novo son la evolución del control de la glucemia y la PA, en nuestro caso determinado por el número de fármacos requeridos para controlar la PA. También hemos encontrado que los valores de creatinina sérica y el rango basal de albúmina eran factores contribuyentes. Como era de esperar, los factores que caracterizaban a un riesgo CV global elevado promovían la aparición de microalbuminuria (23). Según lo descrito con publicaciones anteriores (24), la presencia de albuminuria se acompañó de un porcentaje significativamente más elevado de pacientes con un nivel de aclaramiento de creatinina inferior a 60 ml/min/1.73 m2.

Cuando ya existe enfermedad CV establecida, un incremento progresivo en la excreción urinaria de albúmina fue observado también en pacientes naïve en el estudio HOPE (25), aunque el ramipril redujo el riesgo de nefropatía manifiesta en un 24% en este estudio. Un efecto protector similar parece dudoso después de supresión crónica del SRAA. Un análisis reciente (26) sobre la tasa estimada de filtrado glomerular y la albuminuria como predictores de eventos en pacientes con alto riesgo CV ha mostrado que ambos parámetros mejoran de forma sustancial la estratificación del riesgo de eventos renales. En nuestra experiencia, la microalbuminuria de novo se acompañó de una prevalencia mayor de nuevos eventos CV, indicando que la microalbuminuria de reciente aparición bajo supresión del SRAA continua siendo un buen predictor de morbilidad y mortalidad CV.

En esta coyuntura os podríamos preguntar con propiedad si podemos prevenir el desarrollo de microalbuminuria de novo en pacientes crónicamente suprimidos. Un control más estricto de la PA sería sin duda beneficioso en aquellos pacientes con cifras más elevadas de PA. Sin embargo, la ausencia de beneficio en la prevalencia de microalbuminuria en el estudio ACCORD (15) con una diferencia de 14 mmHg entre ambos brazos de tratamiento sugiere que el control de la PA sistólica por debajo de 120 mmHg no ofrece ningún beneficio. Dicha cifra de PA sistólica fue de 135 mmHg en el estudio ROADMAP (20). El bloqueo dual del SRAA es ampliamente utilizado en la actualidad por los nefrólogos para control la albuminuria, pero los datos del estudio ONTARGET (27) hacen cuestionar la utilidad del doble bloqueo del sistema a la hora de mejorar los resultados de

prevención CV. El papel de la inhibición directa de renina con aliskiren resultó positivo en el estudio AVOID (28) pero son necesarios más datos. Finalmente, los datos sobre la combinación de un IECA o un ARA con bloqueantes aldosterónicos (29,30) han sido positivos, pero valores disminuidos en la tasa estimada de filtrado glomerular podrían impedir su utilización debido al riesgo de hiperkaliemia.

Se deben hacer algunas advertencias sobre nuestro estudio. La primera es que se trata de un análisis retrospectivo. La segunda sería que nuestros datos corresponden a una población hipertensa tanto de pacientes diabéticos como no diabéticos con un elevado riesgo CV global acompañante. De hecho, en aquellos sin eventos CV previos a su llegada, el porcentaje de desarrollo de en esta coyuntura de novo fue únicamente del 10%.

En resumen, la supresión crónica del SRAA parece no mantener de manera consistente su capacidad protectora sobre el desarrollo y la evolución de albuminuria en pacientes hipertensos, tanto diabéticos como no diabéticos. Incluso bajo supresión crónica del SRAA la albuminuria sigue siendo un potente predictor de eventos CV. Estos hallazgos requieren una revisión de las implicaciones terapeúticas de la supresión del SRAA.

Tabla 1. Evolución del control de la presión arterial y variables analíticas

	Momento basal	**Año 1**	**Año 2**	**Año 3**	**p**
PA Sistólica (mmHg)	137.7±18.3	137.4±20.4	137.1±19.2	136.6±20.1	0.686
PA Diastólica (mmHg)	80.0±10.0	79.9±14.8	78.2±10.2	77.4±11.3	<0.001
Colesterol Total (mg/dl)	207.3±34.7	198.1±30.2	190.3±32.3	189.1±35.5	<0.001
HDL-colesterol (mg/dl)	54.9±13.2	55.8±13.5	56.6±14.8	55.8±14.1	0.258
LDL-colesterol (mg/dl)	129.4±31.2	117.5±31.2	110.6±28.9	110.3±30.7	0.008
Triglicéridos (mg/dl)	115.8±58.1	116.8±59.7	117.0±61.5	117.1±56.4	0.699
Creatinina sérica (mg/dl)	0.95±0.29	0.95±0.30	0.95±0.27	0.95±0.29	0.344
Aclaramiento de Creatinina. (ml/min)	99.3±49.6	106.7±45.8	106.0±48.1	105.6±48.7	0.645
Glucose sérica (mg/dl)	108.5±27.4	107.3±28.2	105.8±26.5	107.9±30.0	0.361
Potasio sérico (mEq/l)	4.2±0.4	4.3±0.4	4.3±0.4	4.3±0.5	0.591
Acido úrico sérico (mg/dl)	6.5±10.0	6.0±5.9	5.6±1.5	5.6±1.5	<0.001

Tabla 2. Evolución de la albuminuria y porcentaje de pacientes con normo-, micro- y macroalbuminuria durante el periodo de seguimiento.

	Momento basal	**Año 1**	**Año 2**	**Año 3**	**p**
Total					0.028
Normal	1141 (100)	992 (86.9)	929 (83.6)	946 (82.9)	
Micro	0	142 (12.4)	170 (15.3)	184 (16.1)	
Macro	0	7 (0.6)	12 (1.1)	11 (1.0)	
No Diabetes					0.039
Normal	1054 (100)	929 (88.1)	862 (84.1)	885 (84.0)	
Micro	0	122 (11.6)	154 (15.0)	162 (15.4)	
Macro	0	3 (0.3)	9 (0.9)	7 (0.7)	
Diabetes					0.259
Normal	87 (100)	63 (72.4)	67 (77.9)	61 (70.1)	
Micro	0	20 (23.0)	16 (18.6)	22 (25.3)	
Macro	0	4 (4.6)	3 (3.5)	4 (4.6)	
p DM vs no DM	NA	<0.001	0.049	<0.001	

Normal: . Micro: microalbuminuria. Macro: macroalbuminuria. Ver métodos para las definiciones. En la visita del año 2, los datos de la albuminuria no estaban disponibles en 30 pacientes

Tabla 3. A) Número y porcentaje de pacientes con valores de PA < 140 y 90 mmHg durante el seguimiento del estudio. B) Número de fármacos utilizados en los diferentes grupos.

A	**Momento basal**	**Año** 1	**Año** 2	**Año** 3
Microalbuminúricos en el momento basal	111 (38.0)	130 (44.5)	112 (38.4)	116 (39.7)
Normoalbuminúricos desarrollando micro o microalbuminuria	154 (41.2)	171 (45.7)	149 (39.8)	160 (42.8)
Pacientes mantenidamente normoalbuminúricos	601 (56.8)	585 (55.2)	579 (54.7)	608 (57.4)
P	<0.001	<0.001	<0.001	<0.001

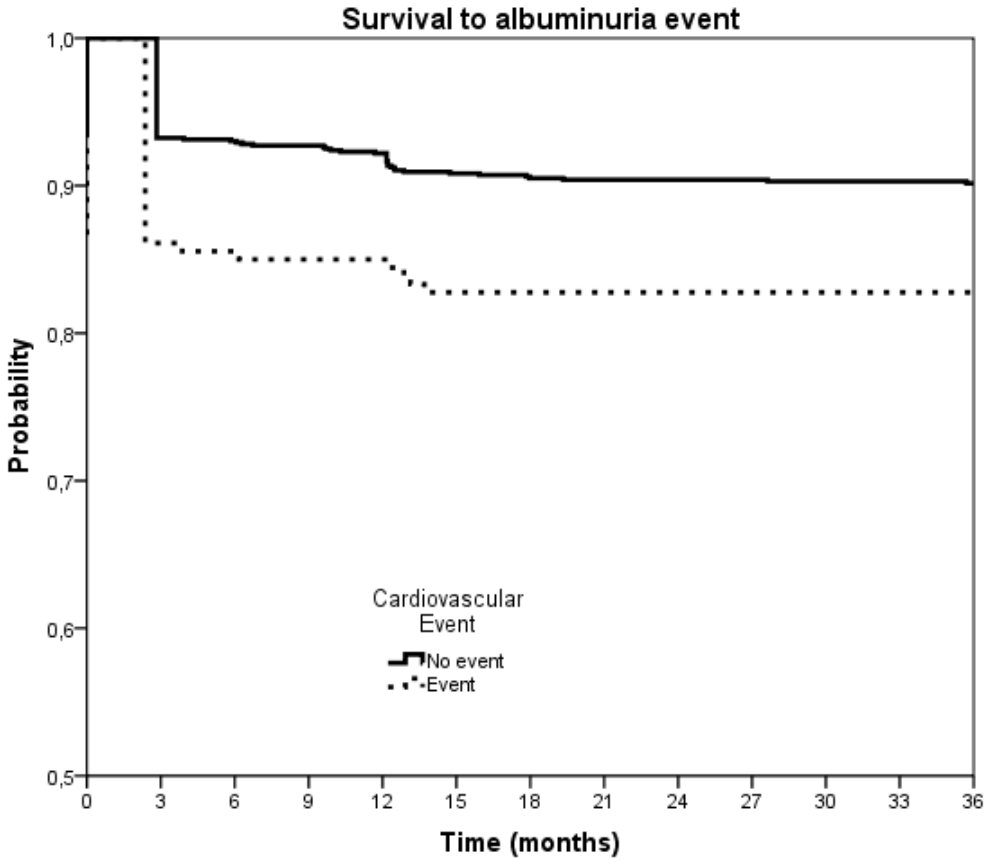
B	**Momento basal**	**Año** 1	**Año** 2	**Año** 3
Microalbuminúricos en el momento basal	2.66±1.25	2.82±1.22	2.77±1.23	2.78±1.22
Normoalbuminúricos desarrollando micro o microalbuminuria	2.74±1.23	2.86±1.15	2.82±1.20	2.79±1.21
Pacientes mantenidamente normoalbuminúricos	2.14±1.17	2.26±1.19	2.22±1.16	2.22±1.11
P	0.008	0.010	0.009	0.009

Tabla 4. Evolución de la albuminuria y porcentaje de pacientes con normo-, micro- y macroalbuminuria de acuerdo a los valores promedio de PA sistólica durante el seguimiento.

	Momento basal	**Año 1**	**Año 2**	**Año 3**	**p**
Total					0.028
Normal	1141 (100)	992 (86.9)	929 (83.6)	946 (82.9)	
Micro	0	142 (12.4)	170 (15.3)	184 (16.1)	
Macro	0	7 (0.6)	12 (1.1)	11 (1.0)	
PAS <130					0.037
Normal	376 (100)	332 (88.6)	321 (88.2)	322 (85.6)	
Micro	0	41 (10.9)	38 (10.4)	50 (13.3)	
Macro	0	2 (0.5)	5 (1.4)	4 (1.1)	
PAS 130-139					0.042
Normal	338 (100)	298 (88.2)	280 (84.8)	287 (84.9)	
Micro	0	40 (11.8)	48 (14.5)	49 (14.5)	
Macro	0	0	2 (0.6)	2 (0.6)	
PAS 140-159					0.053
Normal	343 (100)	294 (85.7)	268 (80.0)	274 (79.9)	
Micro	0	45 (13.1)	63 (18.8)	66 (19.2)	
Macro	0	4 (1.2)	4 (1.2)	3 (0.9)	
PAS ≥160					0.055
Normal	84 (100)	67 (79.8)	60 (73.2)	63 (75.0)	
Micro	0	16 (19.0)	21 (25.6)	19 (22.6)	
Macro	0	1 (1.2)	1 (1.2)	2 (2.4)	
p	NA	0.028	<0.001	0.007	

Normal: . Micro: microalbuminuria. Macro: macroalbuminuria. Ver métodos para las definiciones.

Figura 1. Desarrollo de albuminuria de novo entre los pacientes hipertensos de acuerdo a sus eventos cardiovasculares previos



TRABAJO 2º: "REVISION DE LOS OBJETIVOS RENALES, CARDIOVASCULARES Y DE MORTALIDAD EN ESTUDIOS CON ANTIHIPERTENSIVOS EN PACIENTES DIABETICOS"

INTRODUCCION

La coexistencia de hipertensión y diabetes incrementa sustancialmente el riesgo de desarrollar daño renal y la lesión orgánica a otros niveles, provocando un aumento en la incidencia de eventos cardiacos y en la mortalidad cardiovascular (CV) global. La enfermedad renal crónica tiene una alta prevalencia en individuos diabéticos; un reciente análisis de los datos del NHANES evidenció como un 39.6% de la población diagnosticada de diabetes, un 17.7% de los sujetos prediabéticos y un 41.7% de aquellos no diagnosticados de diabetes presentaban enfermedad renal crónica (31). La disfunción renal, incluyendo la proteinuria y la microalbuminuria, es un predictor de eventos CV y de mortalidad tanto CV como por todas las causas (32-35). Un reciente meta-análisis en una cohorte de población general donde se incluyeron más de un millón de participantes ha proporcionado sólidas evidencias acerca de la relación directa entre la disfunción renal y el riesgo CV. Una tasa estimada de filtración glomerular <60 ml/min/1.73 m^2 y un cociente albúmina/creatinina≥1.1 mg/mmol (≥10 mg/g) fueron ambos factores predictores independientes del riesgo de mortalidad en la población general. Los dos parámetros incrementaron la mortalidad de una manera exponencial, sin evidencia de interacción. Este estudio confirma que una tasa estimada de filtrado glomerular de 60 ml/min/1.73 m^2 y el límite inferior de albuminuria normal-alta (1.1 mg/mmol [10 mg/g]) son puntos de corte adecuados para la valoración correcta del riesgo y para la definición y estratificación de la enfermedad renal crónica (36).

Los pacientes diabéticos son probablemente los pacientes hipertensos más difíciles de tratar y, especialmente en aquellos con disfunción renal, el tratamiento en combinación con varios fármacos antihipertensivos es habitualmente necesario. Existe evidencia que los supresores del sistema renina-angiotensina-aldosterona podrían poseer propiedades específicas en lo referente

a la protección renal, y dichos agentes son los preferidos tanto en monoterapia como formando parte de la terapia en combinación (3).

Los tratamientos antihipertensivos han sido evaluados en numerosos grandes estudios randomizados de duración prolongada. Sin embargo, persisten ciertas controversias acerca de la terapia antihipertensiva óptima en los pacientes diabéticos. En esta revisión intentamos revisar y evaluar los estudios recientes considerados como referencia y que han servido de base para el actual conocimiento y manejo de la hipertensión en diabéticos tipo 2. Para ello, nos hemos enfocado en diversos aspectos, incluyendo:

- si los beneficios en términos de mortalidad y morbilidad dependen exclusivamente de los niveles de presión arterial alcanzados con el tratamiento;
- los posibles efectos adversos metabólicos de algunas familias de fármacos antihipertensivos;
- la relación entre objetivos secundarios, especialmente renales, y objetivos primarios, particularmente mortalidad CV y global;
- las dificultades que el uso de la combinación de dos o más fármacos pueden ocasionar en el diseño e interpretación de los estudios clínicos.

El optimismo de final de milenio

Los años finales del siglo XX estuvieron marcados por una serie de estudios que incidieron en la importancia y en los potenciales beneficios de un tratamiento antihipertensivo eficaz en los pacientes con diabetes tipo 2. Uno de los estudios que ha sido considerado como referencia es el UK Prospective Diabetes Study (UKPDS), el cual ha generado abundante evidencia científica publicada. Uno de los más importantes fue el número 28, que comparó los efectos del control estricto de la presión arterial (PA) sobre las complicaciones diabéticas macro y microvasculares en pacientes con diagnóstico reciente de diabetes tipo 2 (37). Un total de 758 pacientes fueron randomizados al grupo de control estricto con un objetivo de PA < 150/85 mmHg, que debían alcanzar utilizando bien

captopril (440 pacientes) o atenolol (358 pacientes), añadiendo otros fármacos si fuera necesario. Otros 390 pacientes fueron asignados a un control menos estricto (objetivo de PA < 180/105 mmHg) utilizando otros tratamientos distintos a betabloqueantes e inhibidores de la enzima convertidora de angiotensina (IECA). Después de un periodo de seguimiento promedio de 8.4 años, la PA alcanzada en los dos grupos fue 144/82 mmHg y 154/87 mmHg en los grupos de control estricto y menos estricto, respectivamente. Sin embargo, las diferencias en los resultados fueron llamativas, con una reducción del 32% en el riesgo de mortalidad relacionada con la diabetes en el grupo de control tensional estricto, acompañado de disminuciones del 44% en ictus y del 34% en todos las enfermedades macrovasculares. A los 6 años de seguimiento, se redujo el riesgo de microalbuminuria (albúmina urinaria ≥50 mg/L) en un 29%, y pocos pacientes mostraron empeoramiento en la retinopatía en el grupo de control estricto. Este estudio evidenció con claridad los beneficios del control de la PA sobre la prevención de complicaciones diabéticas micro y macrovasculares con la utilización de IECA, y los autores concluyeron que el manejo de la PA debería ser una prioridad en el tratamiento de la diabetes tipo 2. Un hecho interesante fue que el 29% de los pacientes del grupo de control estricto necesitaron tres o más fármacos antihipertensivos para alcanzar los objetivos de PA. Un análisis posterior reveló que no existían diferencias significativas en ninguno de los objetivos entre el grupo de captopril y el de atenolol (38). Por último, un estudio de seguimiento a 10 años (39) mostró que, después de haber finalizado el estudio UKPDS, las cifras de PA aumentaron en el grupo de control estricto y disminuyeron en el de control menos estricto, reduciéndose las diferencias en el riesgo entre los dos grupos, volviéndose no significativas. Así, el control óptimo de la PA debe mantenerse para alcanzar los objetivos a largo plazo.

Poco tiempo después del UKPDS se publicó el Captopril Prevention Project (CAPPP), en el cual 10985 pacientes fueron randomizados a recibir bien el IECA captopril o el tratamiento convencional con diuréticos y betabloqueantes. Durante los 6.1 años que duró el periodo de seguimiento, no se encontraron diferencias en la prevención de la mortalidad y morbilidad CV entre la terapia convencional y el captopril (40). Sin embargo, en un subgrupo relativamente

pequeño de 572 pacientes sin diabetes en el momento basal (4.9% del total de la muestra), el objetivo compuesto primario de infarto de miocardio, ictus y mortalidad CV fue sustancialmente inferior en el grupo de captopril (riesgo relativo 0.59), reduciéndose también significativamente la mortalidad total (riesgo relativo 0.54). En este estudio, las divergencias en los resultados no se podían explicar por diferencias en las reducciones de PA; en todo caso las cifras de PA fueron discretamente más bajas con el tratamiento convencional que con captopril en esta cohorte de pacientes diabéticos (41).

Estos dos estudios tienen en común la clara demostración acerca de los considerables beneficios en términos de mortalidad y morbilidad CV que se pueden alcanzar con determinados tratamientos antihipertensivos como los IECA en los pacientes con diabetes. Sin embargo, también ofrecían los primeros datos sobre las controversias que aparecerían con posterioridad sobre los beneficios específicos de las diferentes clases de fármacos antihipertensivos y de sus combinaciones, así como de las dificultades en el diseño de los estudios cuando tenemos un elevado número de tratamientos eficaces disponibles y el tratamiento óptimo de muchos pacientes implicaría la combinación de dos o más fármacos.

Cambio en el nuevo siglo – HOPE, PROGRESS y la controversia

En Enero del año 2000 se publicó el influyente estudio Heart Outcomes Prevention Evaluation (HOPE)(42). Un total de 9297 pacientes de alto riesgo con historia de enfermedad CV o diabetes más algún otro factor de riesgo CV fueron randomizados a recibir el IECA ramipril o placebo durante aproximadamente 4.5 años. Los fármacos del estudio se administraron sobre el tratamiento CV que siguiera el paciente con anterioridad, excepto los supresores del sistema renina-angiotensina-aldosterona (SRAA), los cuales no fueron permitidos a menos que así lo requirieran las condiciones clínicas de los pacientes durante el estudio. Ramipril redujo la incidencia del objetivo primario compuesto (infarto de miocardio, ictus y mortalidad CV) en un 22%, la mortalidad CV en un 26% y la mortalidad por cualquier causa en un 16%. Un hallazgo relevante fue que la

reducción de la PA con ramipril, en comparación con placebo, fue discreta (aproximadamente 3/2 mmHg), descensos que los autores consideraron demasiado pequeños para justificar los resultados obtenidos. Un resultado adicional fue que la incidencia de aparición de diabetes de novo durante el estudio fue marcadamente inferior en el grupo de ramipril, con un riesgo relativo de 0.66. Pronto apareció el análisis de un subgrupo de 3577 pacientes diagnosticados de diabetes en el momento basal (25). La reducción de PA con ramipril fue aún menor en este subgrupo (2.4/1.0 mmHg), pero la disminución del riesgo tendió a ser discretamente mayor que en la población completa del estudio HOPE, con la reducción de un 25% en los objetivos primarios, de un 37% en la mortalidad CV y de un 24% en la mortalidad por cualquier causa, así como un descenso en la incidencia de daño renal establecido de un 24%. Un subanálisis posterior en pacientes con insuficiencia renal leve (43) evidenció que dichos individuos presentaban un marcado incremento en el riesgo de mortalidad tanto CV como global, y que las reducciones del riesgo relativo observadas con ramipril fueron mayores en los sujetos con insuficiencia renal (41% para ambas causas de muerte) que en aquellos sin afectación renal (22% y 10% respectivamente para la mortalidad CV y global).

Con posterioridad al estudio HOPE se publicó el PROGRESS (Preventing Strokes by Lowering Blood Pressure in Patients With Cerebral Ischemia)(44), que inicialmente fue diseñado como un estudio de prevención secundaria de ictus, pero que finalmente tuvo importantes implicaciones especialmente, en lo referente al tratamiento en combinación. 6105 pacientes con historia de ictus o accidente isquémico transitorio fueron randomizados a recibir un tratamiento activo con perindopril (con o sin la asociación del diurético indapamida) o placebo durante un periodo medio de seguimiento de 3.9 años. En global, el tratamiento activo produjo una reducción del 28% en la incidencia de ictus y de un 26% en los eventos CV mayores, con beneficios similares en pacientes tanto hipertensos como no hipertensos. Aproximadamente el 42% de los pacientes fueron tratados con perindopril en monoterapia y un 58% con la combinación perindopril+indapamida. La PA se redujo en 5/3 mmHg con el IECA en monoterapia y en 12/5 mmHg con la combinación. Los resultados en los

pacientes que siguieron tratamiento con la combinación perindopril+indapamida fueron muy llamativos, con una reducción del 43% en el riesgo de ictus y del 40% en el de eventos CV mayores. Los análisis ulteriores en los 761 pacientes con diabetes en el momento basal (45) mostraron un mayor efecto del tratamiento, aunque no estadísticamente significativo, en los diabéticos en comparación con los no diabéticos, con una disminución del riesgo de ictus del 38% y 28% respectivamente, si bien los pacientes diabéticos tratados con la combinación perindopril+indapamida mostraron un descenso sorprendente del 46% en el riesgo de aparición de ictus.

Los resultados de estos estudios confirmaron los beneficios del tratamiento con IECA, hecho reflejado con posterioridad en las guías científicas, apoyando su utilización en los grupos control de los estudios posteriores.

Antagonistas de los receptores de angiotensina II y clortalidona: ¿nuevos desafíos?

Deben ser mencionados dos estudios de los primeros años del sigo XXI. El estudio LIFE (Losartan Intervention For Endpoint Reduction in Hypertension)(46) comparó el tratamiento basado en el antagonista de los receptores de angiotensina II (ARA) losartán con otro basado en atenolol en una población específica de 9193 pacientes con hipertrofia ventricular izquierda e hipertensión (cifra promedio de PA 174/98 mmHg), durante un periodo medio de seguimiento de 4.8 años. La mayoría de los pacientes en ambos grupos seguían tratamiento además con hidroclorotiazida, y podían tomar otros fármacos antihipertensivos si lo precisaban. Se consiguieron importantes aunque similares reducciones en la PA en ambos grupos, alcanzando 30/17 mmHg en el grupo de losartán y 29/17 mmHg en el de atenolol. El riesgo de alcanzar el objetivo compuesto primario (mortalidad CV, infarto de miocardio e ictus) se redujo en un 13% en el grupo de losartán comparado con el grupo de atenolol, con una disminución especialmente representativa del 25% en el riesgo de ictus. La mortalidad global y CV no fue significativamente diferente entre ambos grupos. De manera relevante, la incidencia de aparición de diabetes de

novo fue un 25% menor en el grupo tratado con ARA. En el subgrupo de pacientes diagnosticados de diabetes en el momento basal, el tratamiento con losartán se asoció con una reducción del 24% en los objetivos primarios, así como con descensos significativos del 37% y del 39% en la mortalidad CV y global, respectivamente (47). En subanálisis posteriores llevados a cabo en los sujetos diabéticos, tanto el nivel de albuminuria basal como la reducción de la excreción urinaria de albúmina durante el tratamiento fueron predictores de eventos CV. La albuminuria disminuyó más con losartán que con atenolol, y únicamente en los pacientes en el quartil más alto de microalbuminuria en el momento basal se observaron reducciones significativas en la mortalidad CV y global (48,49).

Los resultados del estudio LIFE han sido objeto de importantes discusiones, fundamentalmente centradas en la utilización del atenolol como un comparador activo. Una revisión sistemática concluyó que los betabloqueantes estudiados (fundamentalmente el atenolol) no tenían efecto beneficioso sobre la enfermedad coronaria ni en la mortalidad global al compararlos con placebo, presentando únicamente un discreto beneficio sobre el ictus (50). Otra revisión afirmó en sus conclusiones, de manera similar al artículo previo, que el atenolol tampoco aportaba un efecto mayor que placebo en los resultados sobre infarto de miocardio y mortalidad, tanto CV como por cualquier otra causa, a pesar de reducir de manera sustancial la PA (51). Los autores, entre los que se encontraba uno de los firmantes del estudio LIFE, concluyeron que estos resultados hacían poner en duda el papel del atenolol como fármaco de referencia en los estudios de hipertensión. Otra consideración necesaria sería que existe evidencia de que probablemente los betabloqueantes, especialmente usados en combinación con los diuréticos tiazídicos, pueden afectar negativamente a la homeostasis de la glucosa (52,53). En el estudio prospectivo ARIC, los sujetos con hipertensión que seguían tratamiento con betabloqueantes presentaron un riesgo de desarrollar diabetes un 28% mayor que aquellos individuos hipertensos que no tomaban ninguna medicación antihipertensiva (54). Esta es una proporción similar al 25% de diferencia en la incidencia de diabetes de novo entre losartán y atenolol en el estudio LIFE (46).

El mayor de todos los megaestudios de hipertensión [Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT)](55), también fue uno de los más controvertidos, recibiendo numerosas críticas y comentarios, que fueron respondidas de manera temprana por los autores (56,57). El estudio comparó el diurético tiazídico clortalidona con el alfabloqueante doxazosina, amlodipino y lisinopril en 42418 pacientes hipertensos de alto riesgo CV. El brazo de tratamiento con doxazosina fue interrumpido de manera precoz, fundamentalmente debido a un riesgo cercano al doble de presentar fallo cardiaco, junto a un riesgo significativamente aumentado de ictus y de los objetivos compuestos de enfermedad CV (58,59). De manera relevante, no hubo diferencias entre los grupos de doxazosina y clortalidona tanto en los objetivos compuestos primarios del estudio (enfermedad coronaria fatal e infarto de miocardio no fatal) como en la mortalidad por cualquier causa, a pesar de que hubo >2000 muertes en los dos grupos durante los 3.3 años del periodo medio de seguimiento.

El resultado principal del ALLHAT fueron que la clortalidona no se diferenció del amlodipino y del lisinopril en lo relativo a sus efectos sobre el objetivo primario, siendo superior que los otros fármacos para algunos objetivos secundarios, incluyendo la insuficiencia cardiaca. Los comentarios y críticas se centraban en muchos aspectos del diseño del estudio, incluyendo el uso de atenolol como tratamiento de segundo escalón en todos los grupos, que propició combinaciones inusuales en muchos pacientes, como la de lisinopril y atenolol (56,57), así como por la dosis baja del IECA recibida en la mayoría de los pacientes (60). Una de las principales preocupaciones, sin embargo, fue el incremento observado en los niveles de glucosa plasmática en ayunas y en la incidencia de diabetes de novo en los pacientes tratados con diuréticos (61-63). En los sujetos sin diabetes en el momento basal, las cifras de glucemia en ayunas se incrementaron en 8.5 mg/dL en el grupo de la clortalidona, comparado con los 3.5 mg/dL en el grupo de lisinopril, siendo el odds ratio para diabetes de novo de 0.55 (95% IC 0.431–0.704, p <0.001) a favor del IECA tras compararlo con el diurético (63).

Muchos otros estudio han apuntado el riesgo de efectos metabólicos adversos asociados con el tratamiento diurético (y betabloqueante). En los 14120 pacientes no diabéticos del estudio ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial)(64), el riesgo de diabetes de novo fue sustancialmente inferior con el régimen amlodipino±perindopril que con el atenolol±tiazida (hazard ratio 0.66, 95% IC 0.59–0.74). En un meta-análisis en red que incluyó 22 estudios, los odds ratios de diabetes de nueva aparición con supresores del SRAA, comparados con diuréticos, fue de 0.57 para los ARA y 0.67 para los IECA (65). Se han propuestos diversos mecanismos para explicar la alteración en el perfil glucémico producida por los diuréticos (66), estando la hipokaliemia habitualmente implicada. En los pacientes no diabéticos del estudio SHEP (Systolic Hypertension in the Elderly Program), la tasa de incidencia de diabetes fue más del doble con clortalidona que con placebo, con una reducción significativa del riesgo, aunque no llegó a eliminarse, tras ajustar para las modificaciones en el potasio plasmático (67). La hipokaliemia puede producir una disminución en la respuesta a la glucosa de las células β pancreáticas y una reducción en la perfusión del músculo, incrementando el contenido graso hepático y el estrés oxidativo vascular, que de manera conjunta pueden alterar el metabolismo de la glucosa (66, 68-72). El uso de tiazidas en combinación con IECA puede minimizar la aparición de hipokaliemia y la intolerancia a la glucosa (38), aunque este efecto no se evidenció cuando el ARA losartán se combinó con hidroclorotiazida en el estudio STAR (The Study of Trandolapril/Verapamil SR and Insulin Resistance)(73).

Supresores del SRAA y enfermedad renal

La nefropatía ha sido reconocida desde hace tiempo como una importante complicación de la diabetes, siendo la hipertensión y la diabetes las causas más comunes de enfermedad renal crónica (ERC)(74,75). El empeoramiento de la función renal conduce a un marcado incremento en el riesgo de presentar mortalidad de causa CV (21) (Figura 1), y las complejas interacciones entre enfermedad CV, diabetes y ERC son cada vez más tenidas en cuenta, aunque siguen aún sin ser comprendidas en su totalidad (36,75,76). Se acepta de manera

generalizada el beneficio que el bloqueo del SRAA tiene sobre los eventos renales; en esta línea, una serie de meta-análisis han mostrado que los IECA pueden prevenir la aparición de microalbuminuria de novo, la progresión a macroalbuminuria y reducir la mortalidad por cualquier causa en pacientes con nefropatía diabética, y que los ARA únicamente poseen propiedades nefroprotectoras (77-81). Durante los últimos 10 años, se han publicado una serie de estudios randomizados placebo-control en población general que incluyen pacientes diabéticos, con o sin nefropatía, tratados con ARA. Las características de estos estudios están resumidas en la Tabla I, incluyendo el número total de muertes que ocurrieron en cada estudio, que es un indicador del poder del estudio para detectar el beneficio del tratamiento activo sobre la mortalidad. Se describe igualmente la tasa aproximada de mortalidad en el grupo placebo de cada estudio, como una medida de la situación del riesgo en la población general. Los nombres completos de los estudios están reflejados en el pie de página de la Tabla I, y los resultados principales están resumidos en la Tabla II.

Los estudios IDNT (The Irbesartan in Diabetic Nephropathy Trial) (8) y RENAAL (Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy) (7) incluyeron pacientes con diabetes tipo 2 y nefropatía. En ambos estudios, los tratamientos randomizados fueron administrados adicionalmente a su medicación antihipertensiva habitual, que excluía IECA, ARA y, en el caso del IDNT, calcioantagonistas. En el estudio IDNT, el tratamiento con irbesartán se asoció con un 20% de reducción, en comparación con placebo, en los objetivos compuestos renales primarios (duplicación de la cifra de creatinina plasmática, estadios finales de enfermedad renal y todas las causas de mortalidad), fundamentalmente debido a la reducción del 33% en el porcentaje de pacientes que duplicaron los niveles de creatinina sérica (Tabla II). Los estadios finales de la enfermedad renal se redujeron en un 23%, pero la diferencia no logró alcanzar significancia estadística ($p=0.07$). Los resultados renales en el grupo de amlodipino fueron similares a placebo. El estudio RENAAL fue detenido prematuramente por razones éticas debido a la exclusión de los IECA como tratamiento de base permitido en el diseño del

estudio. Durante los 3.4 años de seguimiento promedio, losartán produjo una reducción significativa del 16% en los objetivos renales primarios (idénticos a los del IDNT), con reducciones significativas tanto en el porcentaje de sujetos que duplicaron las cifras de creatinina plasmática como en los que alcanzaron estadios finales de enfermedad renal (Tabla II). Losartán también consiguió un descenso promedio de los niveles de proteinuria (medido como cociente albúmina urinaria/creatinina) de un 35% desde los valores iniciales, mientras que dicho cociente tendió a incrementarse en el grupo placebo ($p<0.001$ para el efecto del tratamiento). A pesar de los beneficios renales alcanzados en ambos estudios, el tratamiento con ARA no produjo ninguna mejoría sustancial o significativa en el riesgo de eventos CV o en la mortalidad tanto CV como global. En el estudio IDNT, irbesartán consiguió una reducción del 28% en la aparición de insuficiencia cardiaca, pero no mostró mejoría sobre el infarto de miocardio, ictus o la mortalidad CV y por cualquier causa (la cual se incrementó, de hecho, en un 8%). Estos datos contrastan con el efecto del amlodipino, el cual produjo una reducción significativa del 42% en el riesgo de infarto de miocardio y descensos no significativos del 35% y 21% respectivamente en los de ictus y mortalidad CV, a pesar de que no se evidenció ningún efecto beneficioso renal (87).

El IRMA 2 (Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group)(82) fue un pequeño estudio que comparó dos dosis de irbesartán con placebo en pacientes con diabetes tipo 2 y microalbuminuria persistente, los cuales podían recibir otra medicación antihipertensiva aparte de ARA o IECA. El objetivo primario de eficacia fue la aparición de nefropatía establecida, definida como una tasa de excreción urinaria de albúmina >200 μg por minuto y un aumento ≥30% respecto a los valores basales. Este objetivo fue alcanzado por 30 pacientes del grupo placebo, 19 del grupo de irbesartán 150 mg y 10 del grupo de irbesartán 300 mg, con unos hazard ratios correspondientes de 0.61 (NS) y 0.30 ($p<0.001$), respectivamente. El nivel de excreción urinaria de albúmina se redujo en un 38% en el grupo de dosis de 300 mg de irbesartán en comparación con el 2% en el grupo placebo ($p<0.001$). Ocho personas fallecieron en el grupo

de las dosis altas de ARA en comparación con las cinco que muertes del grupo placebo.

En contraste con estos tres estudios anteriores, los pacientes del estudio TRASCEND (The Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease) (83,88) ya presentaban enfermedad CV establecida o diabetes con daño orgánico avanzado, pero sin macroalbuminuria o insuficiencia cardiaca. La intolerancia a IECA fue un criterio de inclusión; otros fármacos antihipertensivos estaban permitidos, incluyendo los ARA no estudiados, aunque únicamente los tomaban <10% de los pacientes. El objetivo renal primario fue la combinación de diálisis, trasplante renal, duplicación de la creatinina sérica y muerte, obteniéndose porcentajes similares en los dos grupos. Sin embargo, la duplicación de la creatinina plasmática ocurrió de manera significativamente más frecuente con telmisartán que con placebo (hazard ratio 1.59, p = 0.031), y un número significativamente mayor de pacientes presentaron una reducción en la tasa estimada de filtrado glomerular con telmisartán. Por otro lado, entre los sujetos con microalbuminuria en el momento basal, la progresión a macroalbuminuria se redujo de manera importante con telmisartán en un 42% (p=0.018). Sin embargo, telmisartán no presentó efectos relevantes en los objetivos principales compuestos cardiovasculares o en la mortalidad global y CV. Los autores concluyeron que el ARA no ofrecía beneficio renal en población intolerante a IECA con riesgo CV elevado, pero sin macroalbuminuria (88).

El siguiente estudio en este campo es un análisis combinado de objetivos renales en los tres estudios DIRECT, que fueron diseñados inicialmente para evaluar el efecto de candesartán sobre la incidencia y progresión de retinopatía en pacientes normoalbuminúricos con diabetes tipo 1 y tipo 2 (84,89,90). El objetivo primario renal fue el desarrollo de microalbuminuria, siendo el porcentaje de cambio en la tasa de excreción urinaria de albúmina el objetivo secundario. Un número similar de pacientes en los dos grupos (ARA y placebo) desarrollaron microalbuminuria en cada uno de los tres estudios, con un hazard ratio (candesartán vs placebo) de 0.95 en el análisis combinado (p=0.60). El

porcentaje anual de cambio en la tasa de excreción urinaria de albúmina fue un 5.5% inferior con candesartán (p=0.024); esto se corresponde con una reducción absoluta de 0.11 µg/min, cifra que los autores describen como modesta y de discutida relevancia clínica. Sin embargo, se debe recordar que este estudio no tuvo suficiente potencia estadística para valorar diferencias en el objetivo renal. El número de muertes fue similar en el grupo de candesartán (51 muertes) que en el de placebo (48 fallecimientos).

El estudio más reciente en esta categoría es el estudio ROADMAP (Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes) (20), en el cual olmesartán fue comparado con placebo en un grupo de 4447 pacientes normoalbuminúricos con diabetes tipo 2. El objetivo primario fue el desarrollo de microalbuminuria de novo. Olmesartán retrasó el tiempo de establecimiento de la microalbuminuria en un 23% (p=0.01), y el número de individuos necesarios a tratar durante 5 años para prevenir un caso de desarrollo de microalbuminuria de novo fue de 41 pacientes. Los objetivos secundarios incluyeron eventos CV y mortalidad CV o por cualquier causa. El número total de eventos CV fue bajo e idéntico con ambos tratamientos. Sin embargo, hubo 15 casos de muerte de origen CV en el grupo de olmesartán comparados con los 3 casos en el grupo placebo (p=0.01). Esta diferencia fue atribuida en parte a un aumento en la proporción de la mortalidad CV con olmesartán en pacientes con enfermedad coronaria establecida, especialmente aquellos en el quartil inferior de PA sistólica y aquellos que mostraron las mayores reducciones de PA con el tratamiento. Los autores del estudio concluyeron que estos hallazgos podrían ser consistentes con el efecto de "curva-J", pero que no se podía achacar a un efecto directo del olmesartán.

Los estudios considerados en este apartado sugieren que el tratamiento con ARA puede retrasar la aparición de microalbuminuria y la progresión a macroalbuminuria, así como reducir la incidencia de manifestaciones más severas de la enfermedad renal, como la duplicación de los valores de creatinina plasmática y la diálisis, aunque existen inconsistencias entre los diferentes objetivos renales. En cualquier caso, ninguno de los estudios ha demostrado un

beneficio significativo de los ARA sobre la mortalidad. La pérdida de la significación de este efecto podría ser esperada en estudios con un número relativamente pequeño de muertes, como el IRMA 2 y el DIRECT. Sin embargo, es de mayor relevancia en aquellos estudios en los que, debido a su gran tamaño muestral y/o al elevado riesgo natural de los pacientes, aparecen un número sustancial de muertes, o, como en el ROADMAP, aparece un incremento en el porcentaje de mortalidad CV en el brazo de tratamiento con ARA. Un análisis reciente (91) de 16 estudios randomizados publicados desde el año 2000 que incluían fundamentalmente pacientes hipertensos concluye que únicamente 3 estudios [ASCOT-BPLA (92), ADVANCE (85) y HYVET (93)] mostraron una reducción significativa en la mortalidad global. Los tratamientos exitosos en estos estudios fueron amlodipino (±perindopril), perindopril+indapamida, e indapamida (±perindopril), respectivamente. Los otros 13 estudios, individualmente y de manera conjunta, no mostraron ningún beneficio en lo relativo a la mortalidad (odds ratio 0.996 para el análisis conjunto).

Combinaciones específicas

Un número elevado de pacientes hipertensos en la práctica clínica reciben tratamiento con más de un fármaco antihipertensivo, siendo la terapia en combinación ampliamente recomendada en las guías de hipertensión de las sociedades científicas. Las combinaciones pueden resultar especialmente importantes en pacientes con diabetes, en los que los objetivos recomendados de PA son un desafío. Debe ser remarcado que en la mayoría de los mayores y más recientes estudios sobre hipertensión, el fármaco del estudio se administraba añadido al tratamiento antihipertensivo habitual, lo que frecuentemente era dejado a criterio del investigador. Por tanto, la mayoría de los estudios evalúan la eficacia de la combinación de fármacos, pero la clase y la dosis de los componentes de la asociación no están correctamente estandarizados. Sin embargo, tres grandes estudios publicados recientemente han evaluado explícitamente las distintas combinaciones, mostrando resultados sorprendentes.

En el gran estudio ONTARGET (Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events)“ (27,16), telmisartán y la combinación de telmisartán y ramipril fueron comparados con ramipril en monoterapia en pacientes con enfermedad CV o diabetes con daño orgánico avanzado. No hubo diferencias significativas entre los grupos de telmisartán y ramipril en los objetivos renales, CV o de mortalidad (Tabla II). Sin embargo, la comparación entre la combinación y la monoterapia con ramipril reveló importantes diferencias.

La combinación fue más efectiva que la monoterapia con ramipril en lo referente a la prevención en la aparición de microalbuminuria de novo y en la progresión de la microalbuminuria preexistente, con unos hazard ratios de 0.88 ($p = 0.003$) y 0.76 ($p = 0.019$), respectivamente. Por otro lado, el objetivo compuesto primario renal (duplicación de la creatinina sérica, diálisis y muerte) apareció de manera significativamente más frecuente con la combinación que con ramipril (hazard ratio 1.09, $p = 0.037$); cada componente fue numéricamente más frecuente con la combinación, con valores de un 20%, 33% y 7%, respectivamente. El descenso en la tasa estimada de filtrado glomerular fue mayor con la combinación que con ramipril ($p<0.001$). Los porcentajes de los objetivos CV y de mortalidad fueron similares entre ambos grupos (combinación y monoterapia). Los efectos adversos renales se describieron de manera significativamente mayor en el grupo de pacientes tratados con la combinación que en el de ramipril (riesgo relativo 1.33, $p<0.001$), y un número mayor de pacientes suspendieron la medicación debido a alteraciones renales en el grupo de la combinación que en el tratado con ramipril (riesgo relativo 1.58, $p<0.005$). Por tanto, la adición de telmisartán a ramipril reduce la incidencia de proteinuria, pero ocasiona un descenso más rápido en la tasa de filtrado glomerular, incrementa la incidencia de eventos renales mayores y no aporta ningún beneficio en términos de eventos CV o mortalidad. Esta es una de las razones por las que las guías no recomiendan esta combinación.

El ADVANCE (Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes) es el mayor estudio llevado a cabo en diabéticos, incluyendo 11140 pacientes. Comparó una combinación a dosis fijas de

perindopril y el diurético indapamida con placebo en pacientes con diabetes tipo 2 e historia de enfermedad CV mayor o al menos uno de los otros factores de riesgo CV (85,94). El tratamiento en combinación redujo el objetivo renal compuesto (aparición de microalbuminuria y de nefropatía de novo, duplicación de las cifras de creatinina sérica y estadios finales de enfermedad renal) en un 21% (hazard ratio 0.79, p <0.0001). Se observaron asimismo reducciones en la aparición de microalbuminuria de novo (21%) y en la progresión desde microalbuminuria a macroalbuminuria (31%). El número de individuos necesarios a tratar durante 5 años para prevenir un caso de desarrollo de microalbuminuria de novo en el ADVANCE fue de 16 pacientes, que puede ser comparado con los correspondientes 41 sujetos necesarios en el estudio ROADMAP (20). Los eventos renales en los últimos estadios de ERC fueron infrecuentes en la población del ADVANCE, y la llegada a las fases finales de la ERC ocurrió con una frecuencia similar tanto en el grupo de combinación como en el de placebo. Sin embargo, la aparición de daño renal de novo o el empeoramiento de la nefropatía previa se redujo en los pacientes con una excreción urinaria de albúmina ≥ 30 (95). En contraste con los estudios con ARA descritos en el apartado anterior, los beneficios renales de la combinación perindopril+indapamida se acompañaron de reducciones significativas en la mortalidad por cualquier causa (en un 14%, p=0.025), mortalidad CV (en un 18%, p=0.027) y eventos coronarios (en un 14%, p=0.020). Se debe incidir en tres hechos reseñables del estudio ADVANCE. En primer lugar, se permitió la utilización de la mayoría de los fármacos antihipertensivos (incluyendo otros supresores del SRAA en un 73% de los pacientes incluidos en el grupo control, hecho que ocurrió por primera vez en este tipo de estudios), exceptuando que los diuréticos tiazídicos no fueron permitidos. La efectividad de los tratamientos autorizados se ejemplificó en el hecho de que la regresión de los niveles de microalbuminuria en al menos un estadio se observó en un 50.2% de los pacientes en el grupo placebo; no obstante, el tratamiento activo proporcionó un beneficio asociado del 16% en la incidencia de regresión (p=0.0017). En segundo lugar, se observaron reducciones significativas en la aparición de eventos renales en todos los subgrupos de pacientes clasificados según la PA en el momento basal, incluyendo aquellos que empezaron el estudio con cifras de PA por debajo

de 125/75 mmHg. De hecho, el menor riesgo para desarrollar eventos renales se vio en el grupo que alcanzó niveles de PA por debajo de 110 mmHg de sistólica y 65 mmHg de diastólica. En tercer lugar, un análisis reciente ha demostrado que el riesgo relativo de mortalidad por cualquier causa se redujo a unos niveles similares en pacientes con y sin nefropatía, y con cualquier estadio de enfermedad renal crónica que presentaran en el momento basal (95). Una cuestión no resuelta en el estudio ADVANCE fue si los beneficios observados eran independientes de la reducción de la PA, dado que la presión arterial alcanzada fue inferior en el grupo de tratamiento activo en un promedio de 5.6 mmHg en la PA sistólica y de 2.2 mmHg en la PA diastólica. Sin embargo, dado que la mayoría de los pacientes diabéticos no alcanzaron sus objetivos de PA (96), la mayor eficacia antihipertensiva de la combinación perindopril+indapamida puede ser considerada como un resultado adicional positivo.

El tercer estudio de este grupo es el ACCOMPLISH (Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients)(86,97), el cual comparó dos combinaciones a dosis fijas, benazepril+amlodipino y benazepril+hidroclorotiazida, en 11506 pacientes con hipertensión e historia de enfermedad CV o diabetes; aproximadamente el 60% (6946) de los pacientes randomizados eran diabéticos. El objetivo primario fue la combinación de eventos CV y mortalidad CV, y el estudio fue suspendido de manera prematura debido a la reducción significativa en este objetivo en el grupo del benazepril+amlodipino (hazard ratio 0.80, $p<0.001$). Hubo una reducción significativa en el compuesto de todos los eventos CV (17%, $p = 0.002$), pero las reducciones en la mortalidad por cualquier causa (10%), mortalidad CV (20%) e ictus (16%) no alcanzaron significación estadística. El objetivo renal primario, compuesto por la duplicación de las cifras de creatinina sérica y la aparición de estadios finales de la enfermedad renal, casi se alcanzó en el grupo del benazepril+amlodipino (hazard ratio 0.52. $p <0.0001$), fundamentalmente debido a la reducción del 49% en la duplicación de los niveles de creatinina plasmática ($p<0.0010$). Del mismo modo que en el estudio ADVANCE, la entrada en diálisis fue infrecuente, ocurriendo en 7 pacientes del grupo de benazepril+amlodipino y en 13 del grupo de benazepril+hidroclorotiazida (NS).

A pesar de la marcada reducción en los eventos en las fases finales de la enfermedad renal con benazepril+amlodipino, la proporción de pacientes con microalbuminuria en el momento basal que regresaron a normoalbuminuria fue sustancialmente menor en este grupo (41.7%) que con benazepril+hidroclorotiazida (68.3%, p=0.0016). Los niveles de PA sistólica entre ambos grupos terapéuticos difirieron en menos de 1 mmHg. En el subgrupo de pacientes diabéticos (98), la incidencia del objetivo primario también fue significativamente menor en el grupo de benazepril+amlodipino con un hazard ratio de 0.79, similar al obtenido en los pacientes no diabéticos (hazard ratio 0.82). Los resultados renales del estudio ACCOMPLISH confirman la necesidad de que los estudios de hipertensión en el futuro consideren de manera conjunta los objetivos CV y renales (97), e indican asimismo que los mecanismos que facilitan la progresión de la enfermedad CV tienen similitudes que pueden conducir a la progresión de la enfermedad renal.

Tratamiento intensivo – más no siempre es lo mejor

El último estudio que consideramos en esta revisión tenía un diseño muy diferente. El reciente estudio ACCORD (Effects of Intensive Glucose Lowering in Type 2 Diabetes)(15) incluyó 4733 pacientes con diabetes tipo 2. No comparó fármacos específicos o combinaciones, si no que evaluó el beneficio de la reducción intensiva de la PA a objetivos de PA sistólica <120 mmHg comparándolo con la terapia estándar con un objetivo de PA sistólica <140 mmHg. En este estudio, los regímenes utilizados en ambos grupos fueron elegidos según el criterio individual de cada investigador, y los tratamientos fueron administrados según un diseño abierto. Fundamentalmente, los fármacos de las cuatro familias principales de antihipertensivos fueron las usadas más frecuentemente en el grupo de tratamiento intensivo (Figura 2). La cifra media de fármacos antihipertensivos transcurrido un año era de 3.4 en el grupo intensivo y 2.1 en el grupo estándar, y al final del estudio el 41% de los pacientes del grupo intensivo estaban tomando ≥4 clases de fármacos (incluyendo inhibidores del SRAA). Las cifras promedio de PA alcanzadas fueron de 119/64

mmHg en el grupo intensivo y 134/71 mmHg en el de tratamiento estándar. No hubo beneficio en el grupo tratado de manera intensiva en el objetivo compuesto primario (infarto de miocardio, ictus y mortalidad CV), ni en la mortalidad global y CV, ni en la frecuencia de alcanzar los estadios finales de la enfermedad renal o de la necesidad de diálisis. Por otra parte, hubo una marcada reducción en la frecuencia de ictus con la terapia intensiva (hazard ratio 0.59, p = 0.01). Una consideración más a reseñar es que el porcentaje de eventos adversos graves fue significativamente mayor en el grupo de tratamiento intensivo. Por tanto, aunque existieron variaciones en la consecución de los diferentes objetivos, la terapia intensiva mostró escasa evidencia a la hora de lograr beneficios y sí algunos datos de posibles efectos deletéreos.

Al menos cuatro puntos emergen con claridad del grupo dispar de estudios presentados en lo concerniente al tratamiento en combinación y los objetivos de PA. En primer lugar, los efectos del tratamiento pueden sufrir variaciones importantes en función de los distintos objetivos. En segundo lugar, las combinaciones de fármacos antihipertensivos difieren en su capacidad para prevenir eventos CV y renales mayores, incluso aunque produzcan descensos similares de la PA. En tercer lugar, la adición de otros fármacos antihipertensivos en pacientes que ya están en tratamiento con uno o más drogas podrían no mejorar los resultados renales y de mortalidad, aunque consigan mayores reducciones de PA. El descenso intensivo de la PA sistólica a cifras <120 mmHg utilizando combinaciones y dosis “ad hoc” en el estudio ACCORD no redujo los eventos renales ni la mortalidad en comparación con la terapia estándar. Finalmente, el único tratamiento que proporcionó prevención primaria y secundaria sobre los eventos renales, junto con un beneficio significativo en términos de mortalidad global y CV, fue la combinación perindopril+amlodipino en el estudio ADVANCE. Este estudio puede ser considerado como el que mejor se ajusta a la reciente revisión de las guías de la Sociedad Europea de Hipertensión en lo referente a la consecución de los objetivos de PA, utilización de una combinación adecuada y obtención simultánea de protección en el riñón y en el sistema cardiovascular (99).

CONCLUSIONES

En conjunto, los resultados de los estudios revisados apoyan el concepto de que la reducción agresiva de la presión arterial es un elemento vital en el manejo de los pacientes con diabetes tipo 2, especialmente si presentan evidencia de daño renal. Sin embargo, es evidente que los fármacos antihipertensivos y las combinaciones difieren de manera sustancial en sus efectos, particularmente en lo referente a su capacidad de reducir la mortalidad, y estas diferencias pueden ser especialmente importantes en los pacientes diabéticos. Fármacos como los betabloqueantes y los diuréticos tiazídicos podrían tener efectos metabólicos adversos y no serían la elección ideal en pacientes con diabetes tipo 2, o con riesgo de desarrollar la enfermedad. La utilización casi universal de más de una clase de fármaco para conseguir el objetivo de presión arterial en pacientes diabéticos tiene implicaciones importantes en el diseño y en la interpretación de los estudios clínicos. Los efectos beneficiosos y adversos de un fármaco pueden estar acentuados o disminuidos por el uso de terapias concomitantes, pero los tipos y las dosis de las terapias habituales habitualmente no están estandarizadas en los estudios. Una evaluación explícita de las combinaciones a dosis fijas está aún en sus primeras etapas, pero ya ha se han evidenciado importantes diferencias en los resultados gracias a su utilización, incluso cuando el efecto sobre la presión arterial sea el mismo. Finalmente, la estrategia de añadir fármacos adicionales a pacientes que ya se encuentran recibiendo dos o más drogas antihipertensivas en un esfuerzo de conseguir cifras “aún más bajas” de presión arterial puede ser contraproducente.

La falta de concordancia entre los diferentes objetivos renales y entre éstos y los objetivos de mortalidad ha quedado demostrada en esta revisión, estando en consonancia con las dudas expresadas sobre el uso de la proteinuria como indicador de la evolución de la enfermedad renal (100,101). Los porcentajes de pacientes que alcanzan los estadios finales de insuficiencia renal o que precisan diálisis podrían tener un valor limitado, dado que estos resultados son relativamente infrecuentes, y los pacientes con macroalbuminuria tiene mayor probabilidad de fallecer que de progresar a una situación de fracaso renal (21).

Por último, tanto la mortalidad por cualquier causa como la debida a enfermedad CV son los objetivos más fiables en los estudios, en tanto en cuanto sólo un limitado número de subgrupos de estos estudios han demostrado una reducción simultánea de la microalbuminuria y de la mortalidad en pacientes diabéticos.

Tabla I. Características de los grandes estudios randomizados con objetivos renales que han incluido pacientes con diabetes mellitus

Estudio	Características de los pacientes	Tratamientos	Seguimiento (años)	PA basal (mmHg)	Diferencia de PA vs control (mmHg)	Total de muertes (porcentaje aproximado)[a]
Monoterapia vs placebo						
IDNT (N = 1715) [8]	DM tipo 2 + nefropatía	Irbesartan (N = 579) Placebo (N = 569) Amlodipino (N = 567)	2.6	159/87	-3.3	263 (55)
RENAAL (N = 1513) [7]	DM tipo 2 + nefropatía	Losartan (N = 751) Placebo (N = 762)	3.4	153/82	-2	313 (60)
IRMA 2 (N = 590) [82]	DM tipo 2 + microalbuminuria persistente	Irbesartan 150 mg (N = 195) Irbesartan 300 mg (N = 195) Placebo (N = 201)	2.0	153/90	-3	4 (2.5)
TRANSCEND (N = 5927) [83]	Enfermedad Cardiovascular o DM con daño orgánico	Telmisartan (N = 2954) Placebo (N = 2972)	4.7	141/82	-4	713 (25)
DIRECT-Renal (N = 5231) [59]	DM tipo 1 y tipo 2, normoalbuminuria	Candesartan (N = 2613) Placebo (N = 2618)	4.7	118/73	-3.3	99 (4)
ROADMAP (N = 4 447) [20]	DM tipo 2, normoalbuminuria + ≥1 factor de riesgo cardiovascular	Olmesartan (N = 2232) Placebo (N = 2215)	3.2	136/81	-3.0	41 (2.1)

Tratamiento en combinación						
ONTARGET (N = 25 620) [27]	Enfermedad Cardiovascular o DM con daño orgánico	Ramipril (N = 8576) Telmisartan (N = 8542) Ramipril + telmisartan (N = 8502)	4.7	142/82	-2.4 (Combinación vs ramipril)	3068 (25) (todos los grupos)
ADVANCE (N = 11 140) [85]	DM tipo 2 + enfermedad cardiovascular o ≥1 factor de riesgo	Perindopril + indapamida (N =5569) Placebo (N = 5571)	4.3	145/81	-5.6	879 (18)
ACCOMPLISH (N = 11 506) [86]	Hipertensión + enfermedad cardiovascular o DM (en el 60% de los pacientes)	Benazepril + amlodipino (N = 5744) Benazepril + hidroclorotiazida (N = 5762)	3.0	145/80	-1.1 (Ben + Am vs Ben + Hidrocl)	498 (14) (ambos grupos)
Comparación de los objetivos de presión arterial						
ACCORD BP (N = 4733) [15]	DM tipo 2 con riesgo elevado de eventos cardiovascular	Objetivo PA Sistólica <120 mmHg (N = 2362) Objetivo PA Sistólica <140 mmHg (N = 2371)	5.0 (para mortalidad)	139/76	-14.2	249 (10)

[a] Porcentaje aproximado referido al grupo placebo, expresado como muertes por cada 1000 pacientes-año (salvo especificación añadida)

Am: amlodipino; Ben: benazepril; PA: presión arterial (sistólica cuando estaba disponible); DM: diabetes mellitus; Hidrocl: hidroclorotiazida

Nombre de los estudios:

IDNT: Irbesartan Diabetic Nephropathy Trial; RENAAL: Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study; IRMA 2: Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study; TRANSCEND: Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease; DIRECT: Diabetic Retinopathy Candesartan Trials; ROADMAP: Randomized Olmesartan and Diabetes Microalbuminuria Prevention study; ONTARGET: Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation Trial; ACCOMPLISH: Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension; ACCORD BP: Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial.

Tabla II. Resumen de los resultados de los grandes estudios randomizados con objetivos renales que han incluido pacientes con diabetes mellitus

Estudio	Albuminuria		Objetivos renales			Cardiovascular		Mortalidad	
	De novo	Progresión	Objetivos primarios o eventos renales	Duplicación de la cifra de creatinina plasmática	Estadios finales de enfermedad renal o diálisis	Cualquier evento	Ictus	Por cualquier causa	Cardiovascular
Monoterapia vs placebo									
IDNT									
Irbesartan vs placebo	–	–	-20% (p = 0.02)	-33% (p = 0.003)	-23% (NS)	-10% (NS)	+1% (NS)	-8% (NS)	+8% (NS)
Amlodipino vs placebo	–	–	+4% (NS)	+6% (NS)	0% (NS)	0% (NS)	-35% (NS)	-12% (NS)	-21% (NS)
RENAAL Losartan vs placebo	–	-35% en CAC (p = 0.001)	-16% (p = 0.02)	-25% (p = 0.006)	-28% (p = 0.002)	-10% (NS)	–	+2% (NS)	–
IRMA 2 Irbesartan 300 mg vs placebo	–	-38% en albúmina urinaria (p <0.001)	-70% (p <0.001)	–	–	–	–	Irbesartan: 8 Placebo: 5	–
TRANSCEND Telmisartan vs placebo	-	-42% (p = 0.018)	+10% (NS)	+59% (p = 0.031)	-29% (NS)	-8% (NS)	-17% (NS)	+5% (NS)	+3% (NS)
DIRECT-Renal Candesartan vs	-5% (NS) (objetivo renal	–	Asimismo un cambio	–	–	–	–	Candesartan: 51	–

placebo	primario)		de -5.5% en EUA (p = 0.024)					Placebo: 48	
ROADMAP Olmesartan vs placebo	23% de retraso en el tiempo de su establecimiento (p = 0.01) (objetivo primario)	–	–	0% (NS) (23 pacientes en cada grupo)	No observado en ningún paciente	0% (NS)	–	+70% (NS)	+394% (p = 0.01) (Olmesartan: 15 Placebo: 3)
Tratamiento en combinación									
ONTARGET									
Telmisartan vs ramipril	-6% (NS)	-17% (NS)	0% (NS)	+11% (NS)	+7% (NS)	+1% (NS)	-9% (NS)	-2% (NS)	0% (NS)
Combinación vs ramipril	-12% (p = 0.003)	-24% (p = 0.019)	+9% (p = 0.037)	+20% (NS)	+33% (NS)	-1% (NS)	-7% (NS)	+7% (NS)	+4% (NS)
ADVANCE Perindopril + indapamida vs placebo	-21% (p = 0.0001)	-22% (p = 0.001)	-21% (p <0.0001)	+21% (NS)	+18% (NS)	-14% (p = 0.020)	-6% (NS)	-14% (p = 0.025)	-18% (p = 0.027)
ACCOMPLISH Benazepril + amlodipino vs benazepril + hidroclorotiazida	–	–	-48% (p <0.0001)	-49% (p <0.0001)	-47% (NS)	-17% (p = 0.002)	-16% (NS)	-10% (NS)	-20% (NS)
Comparación de los objetivos de									

presión arterial									
ACCORD BP Objetivo <120 mmHg vs objetivo <140 mmHg de PA sistólica	30.2% vs 32.3% (NS)	6.6% vs 8.7% (p = 0.009)	–	24% vs 16% (p <0.001) (únicamente elevación de la creatinina plasmática)	No diferencias significativas	-13% (NS) (únicamente IM no fatal)	- 41% (p = 0.01)	+7% (NS)	+6% (NS)

IM: infarto de miocardio; NS: no significativo; CAC: cociente albúmina/creatinina; EUA: excreción urinaria de albúmina

Figura 1. Riesgo anual de mortalidad cardiovascular (CV) en pacientes con diabetes tipo 2 y diferentes estadios de nefropatía en el UKPDS. Micro: microalbuminuria; Macro: macroalbuminuria; Elev creat: elevación de la creatinina plasmática o tratamiento sustitutivo renal. Datos recogidos de Adler et al. [48].

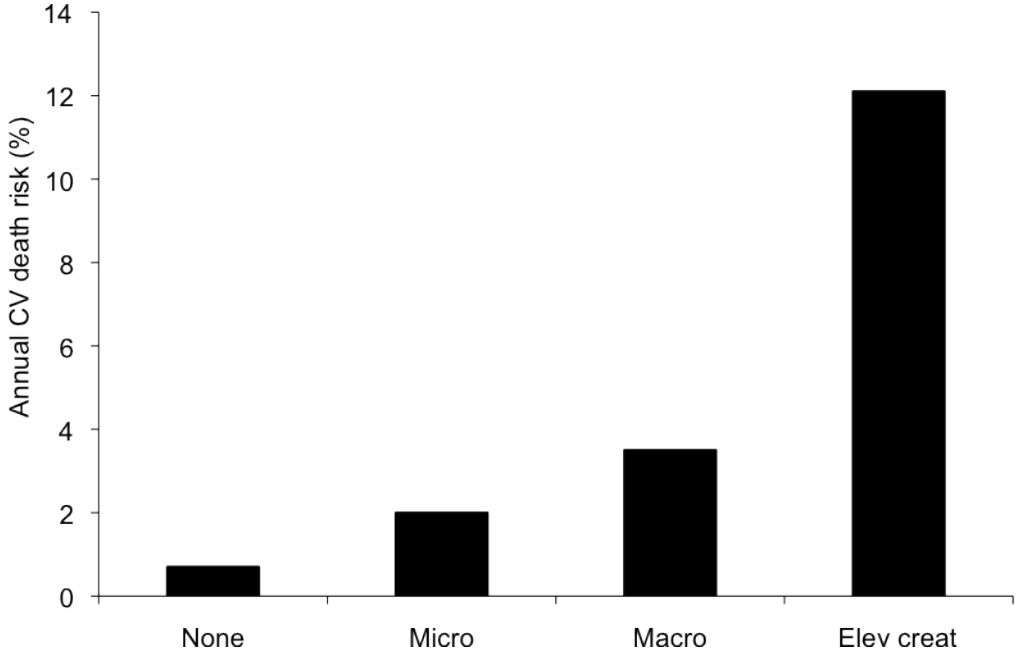
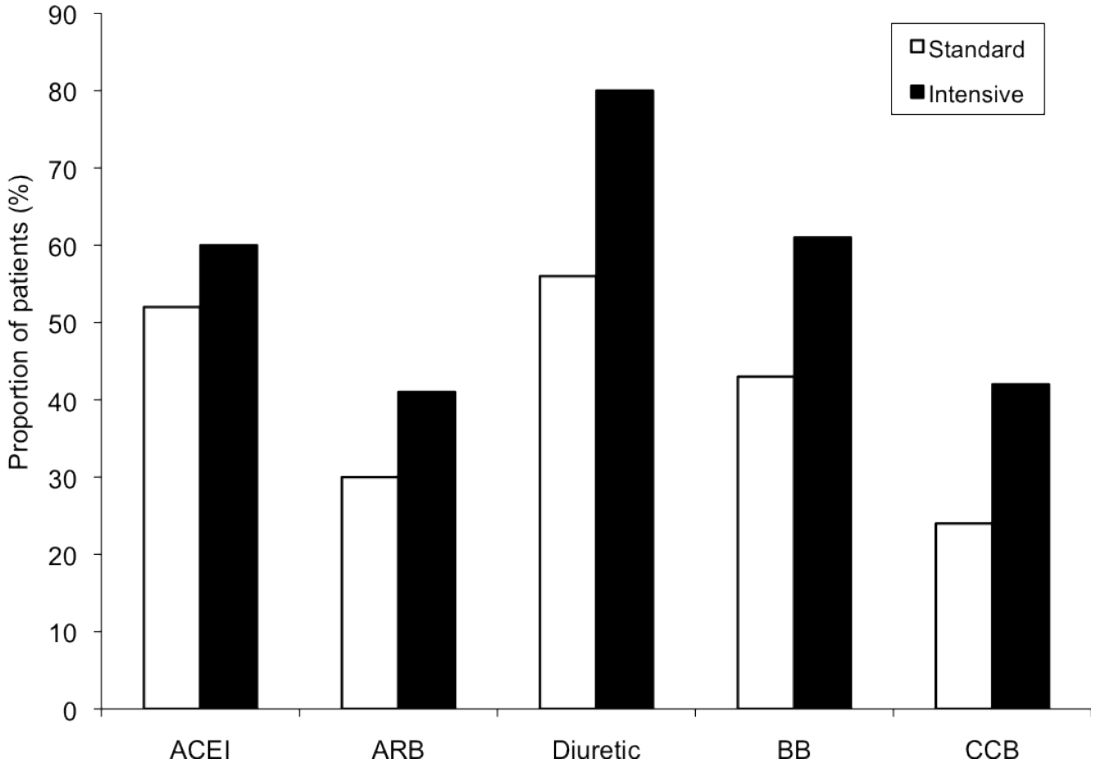


Figura 2. Principales grupos de fármacos antihipertensivos prescritos en la última visita de estudio en los pacientes de los grupos de tratamiento intensivo o estándar en el estudio ACCORD. Los alfa-bloqueantes, reserpina y otros antihipertensivos también se prescribieron en < 25% de los pacientes de cada grupo. ACEI: inhibidores de la enzima convertidora de angiotensina; ARB: antagonistas de los receptores de angiotensina-II; BB: beta-bloqueantes; CCB: antagonistas de los canales de calcio. Datos recogidos del ACCORD Study Group [64].



TRABAJO 3º: "VALIDACION DE UN ESQUEMA TERAPEUTICO PARA EL TRATAMIENTO DE LA HIPERTENSION REFRACTARIA"

INTRODUCCION

La hipertensión refractaria (HR) se define como la presión arterial (PA) que permanece por encima de los objetivos (>140/90 mmHg) a pesar de la utilización simultánea de 3 ó mas fármacos antihipertensivos, uno de ellos un diurético, y todos prescritos a dosis óptimas (102). Aunque la prevalencia exacta es desconocida, varios estudios sugieren que la HR es un problema clínico muy frecuente (103), y se relaciona claramente con un peor pronóstico cardiovascular (CV)(104). Datos recientes de nuestro grupo CARDIORISC (105) obtenidos mediante la monitorización ambulatoria de PA en 24 horas (MAPA) revelan que el 12% de los pacientes hipertensos tratados pueden ser clasificados como refractarios al tratamiento.

El tratamiento de la HR (102) está dirigido a:

- la identificación y modificación de los hábitos de vida que contribuyen a la resistencia al tratamiento, en particular el consumo de sal.
- el diagnóstico preciso y el tratamiento adecuado de las causas secundarias de hipertensión.
- la utilización de regímenes efectivos de combinaciones de distintos fármacos.

Las recomendaciones sobre el tratamiento farmacológico siguen estando mayoritariamente basadas en la práctica clínica dada la falta de acuerdo en los esquemas de combinación de 3 ó 4 fármacos. Por otra parte, los estudios terapéuticos sobre HR son limitados debido al elevado riesgo CV de estos pacientes, que generalmente son excluidos al no poderse suspender la medicación previa (102). Las recomendaciones farmacológicas específicas incluyen la utilización de diuréticos de duración prolongada, antagonistas de los receptores mineralocorticoideos (106-108) o antagonistas de los receptores de endotelina (109). De todas estas opciones terapeúticas, la espironolactona ha demostrado ser una herramienta útil para el control de la PA en pacientes con

HR verdadera, pero no existen recomendaciones claras para aquellos pacientes que no responden a espironolactona (106).

Nosotros hemos examinado la hipótesis de que una triple combinación de fármacos antihipertensivos pudiera ser efectiva en el tratamiento de los pacientes no respondedores a espironolactona. Esta asociación farmacológica consiste en:

- la sustitución del diurético habitual (hidroclorotiazida 50 mg diarios o furosemida 40-80 mg/día) por clortalidona.
- si fuera necesaria, la modificación del antagonista de los canales de calcio por la dosis máxima del calcioantagonista más comúnmente utilizado (amlodipino 10 mg)
- el mantenimiento del resto de fármacos [inhibidores de la enzima convertidora de angiotensina (IECA), antagonistas de los receptores de angiotensina-II (ARA), alfa o betabloqueantes] a la mismas dosis.
- la asociación de un inhibidor directo de renina (aliskiren 300 mg).

METODOS

Diseño del estudio

Hemos llevado a cabo un estudio prospectivo con el objetivo de evaluar la respuesta al bloqueo aldosterónico en pacientes con HR verdadera, y de analizar los efectos de un inhibidor directo de renina, aliskiren, en combinación con 50 mg de clortalidona y 10 mg de amlodipino asociados a las otras medicaciones no diuréticas ni calcioantagonistas, en aquellos pacientes con HR que no respondían a la terapia con espironolactona. Hemos incluido consecutivamente pacientes que llegaron a nuestra Unidad que cumplían los siguientes criterios de inclusión: edad entre 18 y 75 años, cifras de PA con valores medios en MAPA-24 horas > 130/80 mmHg que se encontraran en tratamiento con 3 ó más fármacos (uno de ellos un diurético) a dosis adecuadas, tasa estimada de filtrado glomerular >40 ml/min/1.73 m^2, potasio sérico <4.8 mEq/L e historia previa de intolerancia a espironolactona. Las muestras de sangre y orina fueron obtenidas para la medición de creatinina sérica, tasa estimada de filtrado glomerular (TFGe), glucosa plasmática, colesterol total, HDL y LDL colesterol, triglicéridos, así como

ácido úrico sérico, sodio y potasio. El cociente albúmina/creatinina fue calculado realizando la media de los valores de tres muestras de orina recogidas a primera hora de la mañana. Un MAPA-24 horas fue realizado en el momento basal para confirmar que los pacientes presentaban una verdadera hipertensión refractaria. Este estudio fue aprobado por nuestro comité ético local y todos los participantes dieron su consentimiento informado.

Setenta y seis pacientes cumplieron los criterios de inclusión (periodo de reclutamiento desde Septiembre 2009 a Septiembre 2010) y todos fueron inicialmente tratados con espironolactona 25-50 mg/día (25 mg diarios en aquellos pacientes con TFGe entre 40-60 ml/min/1.73 m^2, 50 mg diarios en los que tenían TFGe >60 ml/min/1.73 m^2), añadido sobre el tratamiento antihipertensivo previo. Después de un periodo de dos meses, se repitieron las mediciones de PA en consulta y de MAPA-24 horas y se solicitó una muestra de sangre para evaluar la creatinina plasmática y la kaliemia. La respuesta a espironolactona fue definida como efectiva si la PA sistólica en MAPA-24 horas disminuyó ≥20 mmHg. En los pacientes no respondedores, se retiró la espironolactona y se inició el esquema que incluía aliskiren 300 mg/día, acompañado de los cambios previamente referidos respecto a la terapia con diuréticos (clortalidona 50 mg) y calcioantagonistas (amlodipino 10 mg), con el resto de la medicación mantenida sin cambios.

Mediciones de PA

La PA fue medida en consulta con un dispositivo semiautomático oscilométrico validado, después de 5 minutos de reposo en posición sentada. Los valores de PA fueron estimados como la media de tres lecturas. A continuación, una MAPA-24 horas fue realizada utilizando un dispositivo oscilométrico no invasivo automático SpaceLabs 90207, programado para registrar la PA en intervalos cada 20 minutos durante el periodo diurno y cada 30 minutos en el periodo nocturno. La mayoría de las mediciones fueron realizadas en días laborales y los pacientes fueron instruidos para mantener su actividad habitual, manteniendo el brazo extendido e inmóvil durante el tiempo de cada inflado del manguito y volviendo a la mañana siguiente para la retirada del dispositivo. Los periodos diurno y nocturno fueron definidos individualmente de acuerdo con los datos

referidos por cada paciente sobre sus horarios de acostarse y levantarse. Ambas mediciones, toma en consulta y MAPA-24 horas, fueron repetidas a los dos meses de iniciar el tratamiento con espironolactona. En aquellos pacientes no respondedores se llevó a cabo la misma metodología nuevamente después de 2 y 4 meses de tratamiento con la triple combinación y nuestro esquema de tratamiento de rescate (ver más arriba).

Análisis estadístico

Los datos son presentados como frecuencias y porcentajes para las variables cualitativas y como la media ± la desviación estándar (o la mediana y rango de interquartiles) para las variables cuantitativas. Las diferencias en las variables del estudio entre los grupos fueron determinadas mediante el coeficiente de Pearson $\chi 2$ para las variables cualitativas y con el test de Student (o el test Mann-Whitney) para las variables cuantitativas. Se consideró significativo un valor de $P<0.05$. El software SPSS para Windows versión 15.0 (SPSS Inc., Chicago, IL, USA) fue utilizado para el análisis estadístico.

RESULTADOS

Abordaje terapeútico

Nuestra población de estudio estaba compuesta por 76 pacientes, cuya media de edad fue 65.3±9.6 años, 52.6% eran mujeres y un 42.1% tenían diabetes. La Tabla 1 resume las características basales de estos pacientes. La Figura 1 muestra la PA sistólica (PAS) y diastólica (PAD) tanto en consulta como en MAPA-24 horas previo y durante la administración de espironolactona. El descenso medio en la PAS y PAD en consulta fue de 21 mmHg (95% IC: 15 a 27 mm Hg) y 7 mmHg (95% IC: 4 a 10 mm Hg), respectivamente ($p<0.001$). La PAS y PAD en MAPA-24 horas disminuyeron una media de 23 mmHg (95% IC: 18 a 27 mm Hg) y 9 mmHg (95% IC: 7 a 11 mm Hg), respectivamente ($p<0.001$). Los análisis de la PA en periodo diurno y nocturno mostraron reducciones similares de la PA.

La tasa de respuesta a la espironolactona fue del 78.9% (n=60). Los pacientes no respondedores a espironolactona (n=16) fueron más jóvenes y presentaban valores más elevados de PA ambulatoria y en consulta en el momento basal que

los sujetos respondedores, sin diferencias en otras características clínicas y bioquímicas entre los dos grupos (Tabla 2). En la Tabla 3 se muestran los valores de PA antes y después de dos meses de tratamiento con espironolactona en respondedores y no respondedores. En los pacientes que no respondieron, se suspendió la espironolactona y se administró aliskiren 300 mg diarios en combinación con amlodipino 10 mg/día y clortalidona 50 mg/día, manteniendo el resto del tratamiento sin modificaciones. Dos meses después, los sujetos que no habían respondido a espironolactona mostraron una reducción media en la PAS y PAD medida en la clínica de 29 mmHg (95% IC: 11 a 48 mm Hg, p=0.004) y 12 mmHg (95% IC: 4 a 20 mm Hg, p=0.005), respectivamente. También se observaron descensos en las cifras de PA ambulatorias, tanto en periodo diurno como nocturno (Tabla 3, Figura 2). Únicamente un paciente (6%) presentó una respuesta inadecuada al tratamiento. En aquellos sujetos que respondieron a esta pauta, se redujo la dosis de clortalidona a 25 mg diarios y se realizó un nuevo MAPA-24 horas dos meses después. Sólo en dos pacientes (13.3%) se aumentó nuevamente la dosis debido a un incremento de la PA mayor de 5 mmHg.

Seguridad y tolerancia

Durante el tratamiento con espironolactona, la creatinina sérica presentó un incremento de 0.92±0.25 mg/dl a 1.00±0.29 mg/dl (p<0.001 para la diferencia) y el potasio sérico desde 4.26±0.45 mEq/L a 4.64±0.50 mEq/L (p<0.001 para la diferencia). El sodio descendió desde 142.4±3.3 mEq/l a 141.5±3.0 mEq/l (p=0.031 para la diferencia). Un total de 12 (15.8%) pacientes presentaron efectos secundarios: ginecomastia (n=6), disfunción eréctil (n=2), hiperkaliemia >6.0 mEq/L (n=3) y 1 caso de incremento de creatinina >30% desde el momento basal.

Durante el tratamiento con aliskiren no se observaron cambios significativos en los parámetros bioquímicos (datos no mostrados).

DISCUSION

Nuestros resultados confirman la capacidad del bloqueante de los receptores de aldosterona espironolactona para controlar la PA en un porcentaje elevado de pacientes con HR verdadera (107). ¿Por qué son los bloqueantes aldosterónicos tan efectivos? Esta clase de fármacos han demostrado ser buenos fármacos antihipertensivos incluso en monoterapia en pacientes con hipertensión esencial (110). Por otro lado, es el tratamiento de elección en el hiperaldosteronismo primario, junto con la adrenalectomía laparoscópica en caso de adenoma (111). Durante los últimos años, evidencias sólidas apoyan el hecho de que el aldosteronismo primario es más prevalente de lo considerado habitualmente. De hecho, entre los pacientes hipertensos de reciente diagnóstico referidos a unidades especializadas de hipertensión, su prevalencia puede ser tan elevada como un 11.2% (111,112). Por tanto, un porcentaje de la hipertensión refractaria podría ser debido a la existencia de una situación de hiperaldosteronismo nunca tratada apropiadamente con fármacos que bloquean los efectos de la aldosterona. De hecho, la incidencia de aldosteronismo primario en pacientes con hipertensión refractaria ha sido estimada incluso en un 14-23% (113) y se ha demostrado una rápida regresión de la hipertrofia ventricular izquierda y de la sobrecarga de volumen intracardiaco después del bloqueo del receptor mineralocorticoideo acompañado de un importante efecto diurético (114). Evidencias recientes también han demostrado que la elevación en los niveles plasmáticos de aldosterona contribuye directamente a la patogénesis de la resistencia insulínica y a los procesos de disfunción endotelial que posteriormente favorecen un remodelado renal y cardiovascular inadecuado, promoviendo así el desarrollo de hipertensión refractaria (115). De este modo, el concepto de añadir espironolactona como primer fármaco en el tratamiento de la hipertensión refractaria está fundamentado y es efectivo como hemos documentado en nuestros últimos datos.

En el porcentaje de pacientes con hipertensión refractaria que no responden a la espironolactona, el incremento en la PA probablemente sea más dependiente de una situación de vasoconstricción marcada que de la existencia de sobrecarga de volumen. Nosotros sugerimos un cambio en la terapia en combinación al añadir

aliskiren 300 mg a amlodipino 10 mg/día y clortalidona 50 mg/día, manteniendo el tratamiento previamente prescrito sin modificaciones (IECA, ARA , alfa y/o betabloqueantes).

La selección de amlodipino 10 mg y clortalidona 50 mg ha estado basada en la excelente capacidad de ambos fármacos para controlar la PA; amlodipino ha demostrado ser muy eficaz a la hora de reducir la PA (116,117), de controlar la variabilidad de la PA (118) y, en combinación con supresores del sistema renina-angiotensina-aldosterona (SRAA), de ofrecer un efecto cardio y nefroprotector en los pacientes hipertensos (86,97). Con respecto a la clortalidona, disponemos de datos que indican una mayor potencia para reducir la PA al compararla con dosis equipotentes de hidrocloriatiazida (119), que pueden traducirse en una mejora del pronóstico renal (120). Clortalidona ha sido reconocida como una herramienta útil en el manejo de hipertensión esencial, más efectiva a la hora de disminuir la PA sistólica que la hidroclorotiazida, como se demostró tras la utilización de MAPA-24 horas (121). Finalmente, nosotros consideramos 50 mg de clortalidona como una dosis adecuada para sustituir el diurético utilizado previamente. Aliskiren ha demostrado ser más potente que ramipril en hipertensión arterial (122,123), que hidroclorotiazida en hipertensos obesos (124), e incluso que irbesartán en pacientes con síndrome metabólico (125). Aliskiren es además una opción válida en el tratamiento de pacientes con hipertensión grado 1 y grado 2, tanto en monoterapia como en combinación con otros antihipertensivos, incluyendo hidroclorotiazida, valsartán o amlodipino (126). En particular, la combinación de aliskiren con amlodipino ha demostrado recientemente en un estudio abierto su capacidad para disminuir la PA, particularmente en pacientes con hipertensión grado 2 (127). Por otra parte, es posible que aliskiren asociado bien a IECA bien a ARA pueda proporcionar un mayor bloqueo del SRAA que la monoterapia con IECA o con ARA, pudiendo conducir a una mejora adicional en los resultados clínicos y de control de la PA (128).

Nuestros datos muestran que el esquema terapéutico utilizado que incluía aliskiren fue positivo, con un único paciente que mostró mala respuesta. Creemos que el papel desempeñado por el resto de medicaciones previas de los

pacientes fue probablemente marginal dado que no se realizó ninguna modificación sobre ellas.

A nuestro entender, este es el primer estudio que ha intentado determinar la eficacia antihipertensiva de un inhibidor directo de renina en combinación con dosis altas de amlodipino y clortalidona en pacientes con hipertensión refractaria que no respondían al bloqueo de los receptores de aldosterona. Una inhibición incompleta del SRAA puede ser responsable de un daño orgánico residual y de un porcentaje de eventos en pacientes con hipertensión, diabetes, enfermedad renal crónica e insuficiencia cardiaca tratados con IECA o ARA (129). La administración tanto de IECA como de ARA se acompaña de un aumento en la actividad de renina plasmática (ARP), que tradicionalmente se ha relacionado con un incremento en el riesgo CV (130). El inhibidor directo de renina de larga duración aliskiren, actuando en el primer paso limitante de la cascada del SRAA, podría prevenir este incremento reactivo de los niveles de ARP cuando se combina con IECA, ARA o diuréticos (129). Además, su elevada afinidad por la renina humana junto con su larga semivida plasmática, comparable a la del amlodipino, y su alta afinidad por el árbol vascular y los glomérulos renales (131) son características adicionales que deben fomentar la utilización de aliskiren en pacientes hipertensos refractarios.

En conclusión, un elevado porcentaje de pacientes con hipertensión refractaria responden favorablemente al bloqueo de los receptores de aldosterona con espironolactona. En aquellos sujetos no respondedores, la adición de aliskiren 300 mg en combinación con un diurético adecuado y dosis altas de amlodipino (más el resto del tratamiento previamente prescrito) parece ser una alternativa adecuada para el control de la hipertensión en estos pacientes.

Tabla 1. Características basales de los pacientes con HR verdadera tratados con espironolactona

Características	Valor
N	76
Edad, años	65.3 ± 9.6
Sexo, % mujeres	52.6
Perímetro abdominal, cm	106±12
IMC, Kg/m^2	31.2 ± 5.3
Duración de la hipertensión, años	20.2 ± 11.0
Fumadores, %	9.2
Diabéticos, %	42.1
Duración de la diabetes, años	8.9 ± 6.4
Enfermedad CV previa, %	23.7
Creatinina, mg/dl	0.92±0.25
Colesterol total, mg/dl	190.7 ± 34.9
HDL-Colesterol, mg/dl	54.7± 13.8
LDL-Colesterol, mg/dl	108,1±32,5
Triglicéridos, mg/dl	152.7 ± 125.9
Excreción urinaria de albúmina (EUA), mg/g	17.5 [6.4-78.7]
EUA > 30 mg/g, %	39.3
Hipertrofia ventricular izquierda por ECG, %	27.6
TFGe por MDRD, ml/min/1.73m^2	80.4±19.7
Velocidad de onda de pulso, m/s	11.2±4.0
PA sistólica (PAS), mmHg	
Consulta	157±19
Casa	160±16
24h	147±13
Periodo diurno	149±13
Periodo nocturno	141±17
Presión Central	143±17
PA diastólica (PAD), mmHg	
Consulta	85±12
Casa	86±10
24h	78±10
Periodo diurno	80±10
Periodo nocturno	74±11
Presión Central	85±13
Número promedio de fármacos antihipertensivos	3.8±0.7
Diuréticos, %	100
IECA/ARA, %	100
Calcioantagonistas, %	69.7
Betabloqueantes, %	47.4
Alphabloqueantes, %	46.1
Vasodilatores directos, %	9.2
Tratamientos concomitantes	

Antidiabéticos orales, %	32.9
Insulina, %	5.3
Estatinas, %	65.8
Fibratos, %	7.9
Antiagregantes plaquetarios, %	26.3

Tabla 2. Diferencias clínicas y bioquímicas entre pacientes respondedores y no respondedores a espironolactona.

Carcaterísticas	Respondedores	No respondedores	p
N	60	16	
Edad, años	66.5 ± 9.4	60.5 ± 9.1	.025
Sexo, % mujeres	58.3	31.3	.054
Perímetro abdominal, cm	106±13	107±11	.810
IMC, Kg/m^2	31.3 ± 5.6	30.5 ± 4.0	.576
Duración de la hipertensión, años	20.9 ± 11.1	17.7 ± 10.1	.309
Fumadores, %	8.3	12.5	.174
Diabéticos, %	41.7	43.8	.881
Duración de la diabetes, años	9.3 ± 6.5	7.5 ± 6.5	.542
Enfermedad CV previa, %	25.0	18.8	.601
Creatinina, mg/dl	0.91±0.27	0.96±0.20	.477
Potasio sérico, mEq/l	4.27±0.50	4.22±0.30	.750
Colesterol total, mg/dl	189.1 ± 35.3	196.4 ± 33.5	.466
HDL-Colesterol, mg/dl	55.1± 12.8	53.3± 17.5	.651
LDL-Colesterol, mg/dl	107.2±33.4	111.5±29.3	.649
Triglicéridos, mg/dl	148.4±114.0	168.9 ± 167.0	.566
Excreción urinaria de albúmina (EUA), mg/g	12.9 [5.4-80.4]	30.5 [9.0-68.6]	.433
EUA > 30 mg/g, %	36.2	50.0	.352
Hipertrofia ventricular izquierda por ECG, %	23.3	43.8	.247
TFGe por MDRD, ml/min/1.73m^2	80.4±20.9	80.6±15.4	.968
Velocidad de onda de pulso, m/s	11.6±3.8	9.9±4.9	.156
PAS, mmHg			
Consulta	154±17	169±24	.004
Casa	159±15	166±18	.092
24h	146±13	148±15	.657
Periodo diurno	148±13	150±12	.592
Periodo nocturno	141±15	142±23	.841

Presión Central	140±15	152±21	.009
PAD, mmHg			
Consulta	83±12	92±13	.007
Casa	85±10	89±11	.177
24h	77±10	81±11	.160
Periodo diurno	79±10	84±11	.106
Periodo nocturno	74±10	76±12	.468
Presión Central	83±13	91±15	.046
Número promedio de fármacos antihipertensivos	3.8±0.8	3.7±0.6	.905

Tabla 3. Cambios en la PA en consulta y ambulatoria después de espironolactona (respondedores y no respondedores) y después de aliskiren (no respondedores a espironolactona)

	Respondedores			No respondedores				
	Pre-espiro	Post-espiro	p[a]	Pre-espiro	Post-espiro	p[a]	Post-alisk	p[b]
PAS en consulta	154±17	127±18	.000	169±24	161±16	.108	141±21	.004
PAD en consulta	83±12	74±11	.000	92±13	89±15	.482	82±12	.005
PAS 24h	146±13	122±15	.000	148±15	142±16	.019	135±14	.011
PAD 24h	77±10	69±11	.000	81±11	73±11	.017	75±10	.015
PAS periodo diurno	148±13	123±16	.000	150±12	146±16	.066	137±16	.013
PAD periodo diurno	79±10	70±11	.000	84±11	76±11	.041	77±11	.011
PAS periodo nocturno	141±15	119±18	.000	142±23	135±21	.019	130±16	.009
PAD periodo noctruno	74±10	66±12	.000	76±12	69±14	.131	69±8	.042

[a]p comparación antes y después del tratamiento con espironolactona.
[b]p comparación antes de espironolactona y después de aliskiren.

Figura 1. Gráfico de cajas representativo de la presión arterial sistólica (arriba) y diastólica (abajo) en consulta y ambulatoria antes (caja clara) y durante (caja oscura) la administración de espironolactona. Los valores de p se refieren a las comparaciones en pareja de t test de PA antes y durante el uso de espironolactona

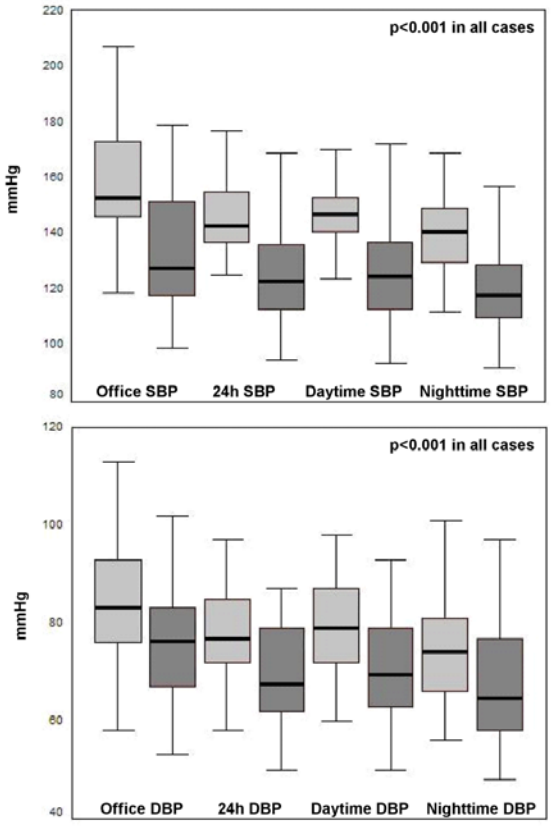
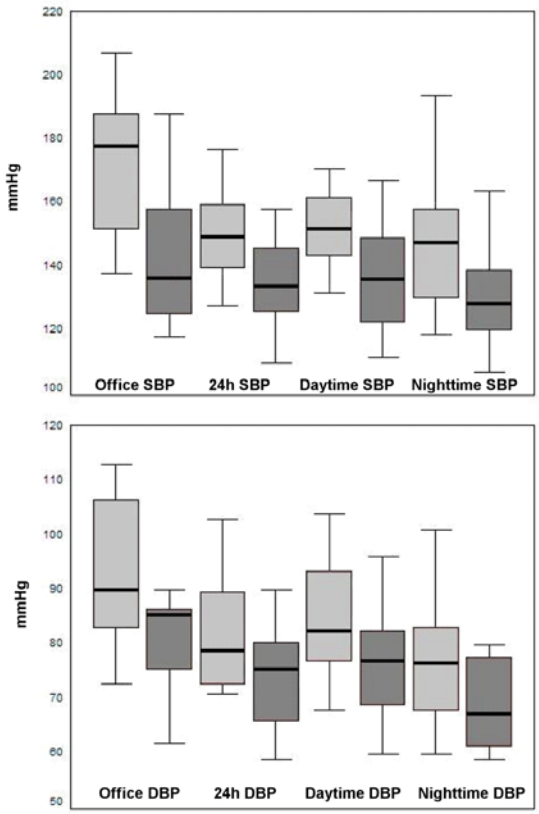


Figura 2. Gráfico de cajas representativo de la presión arterial sistólica (arriba) y diastólica (abajo) en consulta y ambulatoria en el momento basal (caja clara) y durante la administración de aliskiren, amlodipino y clortalidona (caja oscura) en pacientes hipertensos no respondedores a espironolactona



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CONCLUSIONES

1. Disponemos de suficientes evidencias que apoyan la utilización de los supresores del sistema renina-angiotensina-aldosterona en todos los estadios del continuum cardiovascular como primera elección de tratamiento antihipertensivo en todos los pacientes hipertensos, fundamentalmente en los diabéticos, debido a que previenen y retrasan de manera más eficaz la progresión hacia daño orgánico y presentan un mejor perfil metabólico y de seguridad que otras familias de antihipertensivos (como diuréticos y betabloqueantes).
2. Existe una elevada prevalencia de albuminuria en pacientes tratados de manera crónica con supresores del sistema renina-angiotensina-aldosterona. En el análisis llevado a cabo en nuestra Unidad este porcentaje se incrementó durante el periodo de seguimiento del estudio a pesar de un esquema con dosis adecuadas de tratamiento antihipertensivo, apareciendo microalbuminuria de novo en un 16.1% de los pacientes normoalbuminúricos.
3. El desarrollo de microalbuminuria fue particularmente prevalente en pacientes hipertensos de alto riesgo que presentaban eventos previos cardiovasculares o que los desarrollaron a lo largo del seguimiento.
4. Los factores relacionados con el desarrollo de microalbuminuria de novo fueron la evolución en el control de la glucemia y de la presión arterial (medido por el número de fármacos antihipertensivos), así como los valores basales de albuminuria y creatinina plasmática.
5. El grado de control de la presión arterial se mantuvo estable durante el seguimiento, con un 54-56% de los pacientes que alcanzaron los objetivos de control tensional, aunque el mejor control correspondió a los sujetos que permanecieron normoalbuminúricos durante los 3 años analizados. De cualquier modo, el desarrollo de albuminuria ocurrió para cualquier nivel de presión arterial sistólica, desde valores inferiores a 130 mmHg hasta superiores a 160 mmHg.
6. Sin embargo, los datos de numerosos estudios epidemiológicos e intervencionistas apoyan la necesidad de un control estricto de la presión arterial en todos los pacientes hipertensos con objeto de frenar la evolución

del daño orgánico. Esta afirmación es particularmente relevante en sujetos diabéticos tipo 2, especialmente si existe evidencia de afectación renal.

7. Los fármacos antihipertensivos, tanto en monoterapia como en combinación, difieren en sus efectos sobre su capacidad para reducir la mortalidad cardiovascular, siendo estas diferencias especialmente importantes en pacientes diabéticos.
8. Asimismo, existe escasa concordancia entre los objetivos renales y los objetivos de mortalidad en la mayoría de los estudios randomizados sobre terapia antihipertensiva (en particular los que incluyen pacientes diabéticos), siendo más fiables los endpoints que atañen a la mortalidad, dado que únicamente un reducido grupo de subanálisis de los grandes estudios referenciados muestran una reducción simultánea de la albuminuria y la mortalidad. Este hecho puede explicarse, al menos en parte, por la dificultad de analizar los resultados de los estudios que incluyen pautas con varios fármacos antihipertensivos, fundamentalmente combinaciones a dosis fijas, dado que aún no están completamente estandarizadas.
9. En los pacientes con hipertensión refractaria, la utilización de nuevas formas de supresión más intensiva del sistema renina-angiotensina-aldosterona (como espironolactona o aliskiren) han demostrado ser efectivas. En concreto, el uso de bloqueantes aldosterónicos consiguen tasas elevadas de control tensional en este grupo de pacientes con un adecuado perfil de seguridad, probablemente debido a la elevada prevalencia de aldosteronismo primario existente en esta cohorte de sujetos.
10. Sin embargo, datos publicados en los últimos años demuestran cómo el daño orgánico progresa y los eventos CV se siguen produciendo en pacientes tratados con dosis adecuadas de supresores del sistema renina-angiotensina, incluso en aquellos sometidos a bloqueo intensivo del sistema, que asimismo han mostrado evidencias contradictorias en lo referente a su perfil de eventos adversos. Por tanto, son necesarios estudios futuros que confirmen cual es la mejor y más segura forma de mejorar la supresión del sistema renina-angiotensina-aldosterona y, en general, una revisión de las implicaciones terapéuticas de la supresión del sistema renina-angiotensina con el objetivo de

lograr un mejor control de la presión arterial y una mayor reducción en el número de eventos cardiovasculares.

ANEXOS

Los trabajos presentados se basan en los siguientes artículos publicados:

TRABAJO 1º: Cerezo C, Ruilope LM, Segura J, Garcia-Donaire JA, de la Cruz JJ, Banegas JR, Waeber B, Rabelink TJ, Messerli FH. Microalbuminuria breakthrough under chronic renin-angiotensin-aldosterone system suppression. J Hypertens. 2012; 30(1): 204-209.

TRABAJO 2º: García-Donaire JA, Segura J, Cerezo C, Ruilope LM. A review of renal, cardiovascular and mortality endpoints in antihypertensive trials in diabetic patients. Blood Press. 2011; 20(6): 322-334.

TRABAJO 3º: Segura J, Cerezo C, Garcia-Donaire JA, Schmieder RE, Praga M, de la Sierra A, Ruilope LM. Validation of a therapeutic scheme for the treatment of resistant hypertension. J Am Soc Hypertens. 2011; 5(6): 498-504.

Microalbuminuria breakthrough under chronic renin–angiotensin–aldosterone system suppression

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Objectives **Microalbuminuria has been shown to be a potent predictor for future development of cardiovascular and renal events that can be prevented by the use of angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs). Both classes of drugs are now-a-days widely used in the treatment of arterial hypertension since the very early stages of the cardiorenal continuum when only cardiovascular risk factors are detected. We describe here the development of de-novo microalbuminuria in patients chronically treated with either an ACEi or an ARB at adequate doses.**

Methods **We reviewed the evolution of 1433 patients (mean age 60.5 ± 12.4 years, 50.3% men, 6.6% having type 2 diabetes), arriving in our hospital-based Hypertension Unit previously treated for a least 2 years either with an ACEi or an ARB, at adequate doses, alone or in combination with other antihypertensive drugs.**

Results **A total of 184 (16.1%) patients developed new-onset microalbuminuria, whereas macroalbuminuria was detected in 11 (1.0%) patients at the end of follow-up. Albuminuria appeared at any level of blood pressure (BP) from below 130/80 mmHg, albeit the highest percentage was seen when SBP was above 160 mmHg. De-novo microalbuminuria was more frequent in those patients presenting with established cardiovascular disease and predicts the future development of cardiovascular events but was not accompanied by a significant worsening of renal function.**

Conclusion **These data indicate that a reappraisal of renin–angiotensin–aldosterone system (RAAS) suppression is required when microalbuminuria appears in patients under chronic RAAS suppression.** ***J Hypertens*** **30:204–209 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: albuminuria, cardiovascular risk, chronic renin–angiotensin system suppression

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate; RAAS, renin–angiotensin–aldosterone system; UAE, urinary albumin excretion

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Introduction

Microalbuminuria is a predictor for the development of renal and cardiovascular complications in patients with and without diabetes [1,2]. Consequently, screening for microalbuminuria is recommended by guidelines [3,4]. Since the initial description of the capacity of captopril to diminish the amount of proteins excreted in urine [5], the ability of renin–angiotensin–aldosterone system (RAAS) suppression to reduce albuminuria has been amply demonstrated in macroalbuminuria and microalbuminuria. In fact, it is well established that RAAS suppression is required in patients with increased amounts of albumin in urine with the double objective of facilitating blood pressure (BP) control while diminishing the amount of albumin in urine beyond the limit predicted by BP drop [3,4,6]. Such an effect has been shown to protect renal function and to delay the development of end-stage renal disease, particularly in patients with macroalbuminuria [7,8].

Simultaneously, the protective role of RAAS suppression in overt cardiovascular disease was demonstrated in patients with heart failure [9], postmyocardial infarction [10] and in patients with elevated global cardiovascular risk [11]. Such a protection could be particularly important in those patients who concomitantly suffer from established cardiovascular and chronic kidney disease (CKD) [12,13].

All these findings, together with the well documented antihypertensive efficacy of RAAS suppressors [3,4],have led to the wide use of angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) particularly in the early stages of the cardiorenal continuum, when only cardiovascular risk factors are

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detected in the absence of asymptomatic target organ damage and BP is elevated.

Recent data, however, have raised the possibility that cardiorenal disease may still develop under chronic RAAS suppression [14], and the evolution of predictors of cardiorenal disease such as microalbuminuria, under chronic RAAS suppression deserve to be investigated. In this study, we retrospectively review our experience with the evolution of albuminuria in hypertensive patients chronically (more than 5 years) RAAS suppressed.

Methods

We reviewed the evolution of 1433 patients (mean age 60.5 ± 12.4 years, 50.3% men, 6.6% having type 2 diabetics), arriving in our hospital-based Hypertension Unit previously treated for a least 2 years either with an ACEi or an ARB, at adequate doses, alone or in combination with other antihypertensive drugs. Our protocol includes a baseline study followed by a 3-month period during which the best possible control of cardiovascular risk factors is attempted. For the purpose of this study baseline data are those obtained at the end of this 3-month period of stabilization. The presence of secondary forms of arterial hypertension was excluded, and patients were subsequently followed for a minimum period of 3 years with visits to the unit, at least, every 6 months. At the end of this period a group of 1141 patients were normoalbuminuric, whereas the remaining 392 (27.3%) presented albuminuria either micro (94%) or macro (6%). Both forms of albuminuria were more prevalent in diabetic than in nondiabetic patients.

This study contains a retrospective analysis of urinary albumin excretion (UAE) in the 1141 normoalbuminuric patients at baseline who maintained RAAS suppression at apparently adequate doses during the whole length of follow-up analysed.

For this retrospective study we defined 'albuminuria event' as either new-onset microalbuminuria (albumin-to-creatinine ratio 20–200 mg/24 h in men and 30–300 mg/24 h in women) confirmed in at least a second occasion among the 6-monthly determinations performed in three samples of early morning urine or when the last measurement was in the range of macroalbuminuria. BP was estimated by using a validated semiautomated OMRON device in standardized conditions and values represent the mean of three consecutive determinations.

Patients received during the follow-up the highest available dose of an ACEi or an ARB, accompanied by a diuretic or a calcium channel blocker when needed and the combination of the three afterwards if BP remained in values above 140/90 mmHg.

Statistical analysis

Quantitative variables are presented as mean $\pm$ SD since all of them were normally distributed except albuminuria (median and interquartile range). Number and percentage were used for categorical variables. Repeat generalized linear models were used to examine evolution of quantitative variables over time. Friedman test for repeat measurements was used for examining evolution of albuminuria over time. The evolution of albuminuria groups (in percentage) over time was studied by using chi-square test for trend. Kaplan–Meieŕs survival function was used for studying time to first new-onset albuminuria event, comparing groups according to the presence of cardiovascular events through the log-rank test.

Finally, Cox regression was used for identifying variables associated with time to new-onset albuminuria. Independent variables considered were: sex, age (years), diabetes (yes, no), creatinine clearance, serum albumin, calcium, estimated glomerular filtration rate by Cockroft and Modification Diet Renal Disease (MDRD) formulas, serum cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein (LDL)-cholesterol, creatinine, glycaemia, haemoglobin, haematocrit, potassium, sodium, triglycerides, uric acid, number of antihypertensive medications, SBP, DBP, hypertension control ($<$140/90 vs. $\geq$140/90 mmHg), at least one previous cardiovascular disease (CVD) event (coronary heart disease, stroke, peripheral artery disease), CVD events over the study follow-up (presence, absence), and baseline albuminuria groups (normal, high-normal). All variables which were statistically significant ($P < 0.01$) on univariate analyses were introduced in the multivariate models through forward stepwise fashion. Statistical significance was set at two-tailed P value less than 0.05. SPSS version vs. 17.0 (SPSS, Chicago, Illinois, USA) was used for all statistical analyses.

Results

Table 1 contains the baseline and yearly evolution of analytical variables measured, as well as BP levels and measured creatinine clearance in the 1141 patients with normoalbuminuria at baseline. BP remained stable with 54–56% of patients attaining an adequate BP control. A significant drop was observed in total and LDL-cholesterol, whereas serum creatinine value remained stabilized in the absence of changes in measured creatinine clearance values. Out of the total 17.4% could be classified as having chronic kidney disease (CKD) according to a value of measured creatinine clearance below 60 ml/min per 1.73 m^2. This percentage was 16.8% at the end of follow-up (P NS). The presence of micro or macroalbuminuria was accompanied by significantly higher percentages of patients with CKD determined by a diminished measured creatinine clearance ($P < 0.01$ vs. normoalbuminuria), 27.4 and 42.9% at baseline, and 25.3 and 56.9% at the end, respectively (P NS vs. baseline).

All the patients received an ACEi (47%) or an ARB (53%) during the follow-up combined with a second drug in 33.8% (62% diuretic and 30% calcium antagonist) and by the combination of three or more drugs in 42.6% of cases.

Table 1 Evolution of blood pressure control and analytical variables

	Baseline	Year 1	Year 2	Year 3	*P*
SBP (mmHg)	137.7 ± 18.3	137.4 ± 20.4	137.1 ± 19.2	136.6 ± 20.1	0.686
DBP (mmHg)	80.0 ± 10.0	79.9 ± 14.8	78.2 ± 10.2	77.4 ± 11.3	<0.001
Total cholesterol (mg/dl)	207.3 ± 34.7	198.1 ± 30.2	190.3 ± 32.3	189.1 ± 35.5	<0.001
HDL-cholesterol (mg/dl)	54.9 ± 13.2	55.8 ± 13.5	56.6 ± 14.8	55.8 ± 14.1	0.258
LDL-cholesterol (mg/dl)	129.4 ± 31.2	117.5 ± 31.2	110.6 ± 28.9	110.3 ± 30.7	0.008
Triglycerides (mg/dl)	115.8 ± 58.1	116.8 ± 59.7	117.0 ± 61.5	117.1 ± 56.4	0.699
Serum creatinine (mg/dl)	0.95 ± 0.29	0.95 ± 0.30	0.95 ± 0.27	0.95 ± 0.29	0.344
Creatinine clearance (ml/min)	99.3 ± 49.6	106.7 ± 45.8	106.0 ± 48.1	105.6 ± 48.7	0.645
Serum glucose (mg/dl)	108.5 ± 27.4	107.3 ± 28.2	105.8 ± 26.5	107.9 ± 30.0	0.361
Serum potassium (mEq/l)	4.2 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.5	0.591
Serum uric acid (mg/dl)	6.5 ± 10.0	6.0 ± 5.9	5.6 ± 1.5	5.6 ± 1.5	<0.001

HDL, high-density lipoprotein; LDL, low-density lipoprotein,

No patient received aldosterone blockers during the follow-up.

Table 2 shows the rise in albuminuria during the follow-up in the 1141 normoalbuminuric patients. A total of 184 (16.1%) patients developed new-onset microalbuminuria, whereas macroalbuminuria was detected in 11 (1.0%) patients at the end of follow-up (Table 2). We also observed that the probability of not having developed the albuminuria event was decreasing over the 3-year period. Specifically, this probability was 0.918 at 6 months, 0.911 at year 1, 0.892 at year 2, and 0.890 at year 3.

Interestingly, the increase in microalbuminuria throughout the 3-year period mainly occurred in the first year. This may be due to that 171 (15%) out of the 1141 patients normoalbuminuric at baseline were at the high-normal range of albuminuria (10–15 mg/day for men and 20–30 mg/day for women), very close to the microalbuminuria range.

Among these 1141 patients, a total of 180 (15.8%) presented at baseline with established cardiovascular disease characterized by 205 nonfatal events (92 myocardial infarctions, 89 strokes, 24 hospitalizations due to heart failure). During the follow-up a total of 53 patients (4.6%) developed a cardiovascular event (30 myocardial infarctions, 23 strokes, six hospitalizations due to heart failure). Figure 1 shows that the probability of developing new-onset albuminuria event according to the presence or absence of a previous cardiovascular event at arrival in the Unit was significantly higher in those with a previous cardiovascular event. New-onset microalbuminuria was seen in 9.9% of patients without a previous event and in 17.2% ($P = 0.003$) of those with a previous event. During the follow-up, new-onset microalbuminuria was seen more frequently in those presenting new cardiovascular events (18.9 vs. 10.7%, $P = 0.057$).

Table 3 represents the percentage of patients with BP values controlled below 140 and /or 90 mmHg during the follow-up. As can be seen the best control correspond to those remaining normoalbuminuric during the follow-up. Those who presented microalbuminuria at baseline and those developing it during follow-up presented a significantly worse control of BP during the consecutive annual visits. The number of drugs required for control was significantly higher in those arriving with or developing albuminuria during the follow-up. Nevertheless, and as can be seen in Table 4, the development of albuminuria took place at any level of SBP maintained during the follow-up, starting in values below 130 mmHg and ending above 160 mmHg.

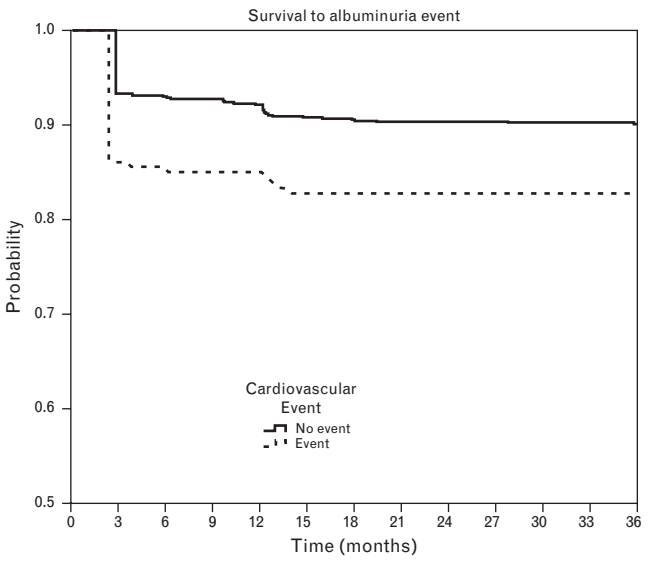
Finally, the multiple regression analysis revealed that the factors related to the development of microalbuminuria

Table 2 Evolution of albuminuria and percentage of patients with normoalbuminuria, microalbuminuria and macroalbuminuria during the follow-up

	Baseline	Year 1	Year 2	Year 3	*P*
Total					0.028
Normal	1141 (100)	992 (86.9)	929 (83.6)	946 (82.9)	
Micro	0	142 (12.4)	170 (15.3)	184 (16.1)	
Macro	0	7 (0.6)	12 (1.1)	11 (1.0)	
No diabetes					0.039
Normal	1054 (100)	929 (88.1)	862 (84.1)	885 (84.0)	
Micro	0	122 (11.6)	154 (15.0)	162 (15.4)	
Macro	0	3 (0.3)	9 (0.9)	7 (0.7)	
Diabetes					0.259
Normal	87 (100)	63 (72.4)	67 (77.9)	61 (70.1)	
Micro	0	20 (23.0)	16 (18.6)	22 (25.3)	
Macro	0	4 (4.6)	3 (3.5)	4 (4.6)	
P, DM vs. no DM	NA	<0.001	0.049	<0.001	

DM, diabetes mellitus; Micro, microalbuminuria; Macro, macroalbuminuria. In the 2-year visit, data on albuminuria were not available for 30 patients.

Fig. 1



Development of new-onset albuminuria among hypertensive patients according to previous cardiovascular events.

were serum glucose [hazard ratio 1.014; confidence interval (CI) 1.007–1.021, $P < 0.001$], serum creatinine (hazard ratio 2.293; CI 1.366–3.850, $P = 0.002$), number of antihypertensive drugs (hazard ratio 1.306; CI 1.056–1.613, $P = 0.014$) and the initial value of albuminuria (normal vs. high-normal) (hazard ratio 3.145; CI 1.886–5.247, $P < 0.001$).

Discussion

The present data show that patients receiving chronic suppression of the RAAS present a high prevalence of albuminuria when they arrive to our Unit. This percentage rises during the follow-up and under adequate conditions of treatment. In fact, de-novo microalbuminuria appeared in 16.1% of normoalbuminuric patients, whereas 1.0% developed macroalbuminuria during 3 years of follow-up in our Unit. The prevalence of microalbuminuria at the end of follow-up is higher (43.4%) to that seen in the ACCORD study [15] in which all the patients were type 2 diabetic and most of them were treated for years either with an ACEi or an ARB. The continuous rise in the amount of albumin lost in urine in many of these patients recalls the data of the ONTARGET study [16] in which albuminuria also rose continuously during the follow-up. Interestingly, almost two-thirds of patients in ONTARGET were previously chronically RAAS suppressed with an ACEi. These data contrast with data obtained in previous trials, such as LIFE [17] and DETAIL [18] in which the initial fall in albumin excretion used to be maintained during the first years of therapy, albeit in DETAIL study the amount of albumin was back to levels similar to those at baseline after 5 years of treatment [18].

Patients presenting with microalbuminuria when arriving to our Unit could correspond to the percentage of patients who do not respond to RAAS suppression. Two nice examples of nonresponders to this type of therapy are seen in BENEDICT [19] and ROADMAP [20] studies in which a significant number of naive patients developed de-novo microalbuminuria while treated with an ACEi and an ARB at adequate doses. Little has been commented about these nonresponders and even less about what to do with them. If prevention of microalbuminuria is relevant here there is an area of great interest for future studies.

Progression from normo to microalbuminuria has been classically recognized to occur in around 2% of diabetic patients per year [21]. Both BENEDICT [19] and ROADMAP [20] demonstrated that the percentage can be higher even in the presence of RAAS suppression and even, as in the case of ROADMAP, in the presence of an excellent BP control [20]. Our data with a minority of patients with diabetes have shown that this percentage attains a 16.1% after 3 years of follow-up and that the appearance of de-novo microalbuminuria is particularly high in those patients presenting with established cardiovascular disease (18.9 vs. 10.7%). Our data also prove that a long-term excellent office BP control does not exclude the development of de-novo microalbuminuria. Our data then indicate that development of microalbuminuria could be particularly prevalent in high-risk hypertensive patients with established cardiovascular disease in whom

Table 3 (a) Number and percentage of patients with BP values less than 140 and 90 mmHg during the follow-up of the study and (b) number of drugs used in the different groups

	Baseline	Year 1	Year 2	Year 3
(a) Number and percentage of patients				
Microalbuminuric at baseline	111 (38.0)	130 (44.5)	112 (38.4)	116 (39.7)
Normoalbuminuric developing micro or microalbuminuria	154 (41.2)	171 (45.7)	149 (39.8)	160 (42.8)
Persistent normoalbuminuric patients	601 (56.8)	585 (55.2)	579 (54.7)	608 (57.4)
P	<0.001	<0.001	<0.001	<0.001
(b) Number of drugs used				
Microalbuminuric at baseline	2.66 ± 1.25	2.82 ± 1.22	2.77 ± 1.23	2.78 ± 1.22
Normoalbuminuric developing micro or microalbuminuria	2.74 ± 1.23	2.86 ± 1.15	2.82 ± 1.20	2.79 ± 1.21
Persistent normoalbuminuric patients	2.14 ± 1.17	2.26 ± 1.19	2.22 ± 1.16	2.22 ± 1.11
P	0.008	0.010	0.009	0.009

Table 4 Evolution of albuminuria and percentage of patients with normoalbuminuria, microalbuminuria and macroalbuminuria according to mean values of SBP during the follow-up

	Baseline	Year 1	Year 2	Year 3	*P*
Total					0.028
Normal	1141 (100)	992 (86.9)	929 (83.6)	946 (82.9)	
Micro	0	142 (12.4)	170 (15.3)	184 (16.1)	
Macro	0	7 (0.6)	12 (1.1)	11 (1.0)	
SBP < 130					0.037
Normal	376 (100)	332 (88.6)	321 (88.2)	322 (85.6)	
Micro	0	41 (10.9)	38 (10.4)	50 (13.3)	
Macro	0	2 (0.5)	5 (1.4)	4 (1.1)	
SBP 130–139					0.042
Normal	338 (100)	298 (88.2)	280 (84.8)	287 (84.9)	
Micro	0	40 (11.8)	48 (14.5)	49 (14.5)	
Macro	0	0	2 (0.6)	2 (0.6)	
SBP 140–159					0.053
Normal	343 (100)	294 (85.7)	268 (80.0)	274 (79.9)	
Micro	0	45 (13.1)	63 (18.8)	66 (19.2)	
Macro	0	4 (1.2)	4 (1.2)	3 (0.9)	
SBP ≥ 160					0.055
Normal	84 (100)	67 (79.8)	60 (73.2)	63 (75.0)	
Micro	0	16 (19.0)	21 (25.6)	19 (22.6)	
Macro	0	1 (1.2)	1 (1.2)	2 (2.4)	
P	NA	0.028	<0.001	0.007	

Micro, microalbuminuria; Macro, macroalbuminuria.

the disease progresses more rapidly than expected in the presence of an 'adequate' RAAS suppression.

In agreement with previous data [22], multiple regression analysis disclosed that factors promoting de-novo development of microalbuminuria are the slope of glycaemia and BP control, in our case determined by the number of drugs required to control BP. We also found that the values of serum creatinine and baseline range of albumin were contributing factors. Factors characterizing a high global cardiovascular risk promote the appearance of microalbuminuria as could be expected [23]. The presence of albuminuria was accompanied as previously described [24] by a significantly higher percentage of patients with a level of measured creatinine clearance inferior to 60 ml/min per 1.73 m^2.

When advanced cardiovascular disease is present, a continuous rise in albumin excreted in urine was also seen in naive patients in HOPE study [25], albeit in this study ramipril lowered the risk of overt nephropathy by 24%. A similar protective effect looks dubious after chronic suppression. A recent analysis [26] of estimated glomerular filtration rate (GFR) and albuminuria as predictors of outcomes in patients with high cardiovascular risk has shown that both parameters greatly improve the risk stratification for renal outcomes. In our experience, de-novo microalbuminuria was accompanied by a higher prevalence of new cardiovascular events indicating that de-novo microalbuminuria under RAAS suppression continues to be a good predictor of cardiovascular morbidity and mortality.

One may appropriately ask at this juncture whether we can prevent the development of de-novo microalbuminuria in patients chronically suppressed. A more strict BP control will no doubt benefit those patients with more elevated levels of BP. However, the absence of benefit for the prevalence of microalbuminuria with a difference of 14 mmHg between arms in the ACCORD study [15] indicates that SBP control below 120 mmHg does not counter benefit. The same figure in the ROADMAP study [20] was 135 mmHg for SBP. Dual RAAS blockade is still being widely used by nephrologists to control albuminuria, but the data of the ONTARGET study [27] make dual RAS blockade of questionable usefulness for cardiovascular outcome. The role of direct renin inhibition with aliskiren was positive in the AVOID study [28] but requires more data. Finally, data on the combination of an ACEi or an ARB with an aldosterone blocker [29,30] have been shown to be positive, but low values of estimated GFR may prevent its use due to the risk of hyperkalaemia.

Our study has some caveats, the first of which is the fact that it is a retrospective study. The second is that our data correspond to a hypertensive population of both diabetic and nondiabetic with a high accompanying global cardiovascular risk. In fact, in those without a previous cardiovascular event at arrival, the percentage developing de-novo microalbuminuria was only 10%.

In summary, chronic RAAS suppression does not seem to consistently maintain its protective capacity on the development and evolution of albuminuria both in diabetic and nondiabetic hypertensive patients. Even on chronic RAAS suppression albuminuria remains a powerful predictor of cardiovascular events. This finding requires a reassessment of the therapeutic implications of RAAS suppression.

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Conflicts of interest

There are no conflicts of interest.

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REVIEW ARTICLE

A review of renal, cardiovascular and mortality endpoints in antihypertensive trials in diabetic patients

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Abstract

Renal disease is highly prevalent in people with type 2 diabetes, and co-existence with hypertension increases the risk of cardiac events and mortality. Despite many large randomized trials, controversies remain regarding optimal antihypertensive therapy in diabetic patients, including whether some classes of antihypertensive drugs have specific renal protective properties, and the relationships between renal, cardiovascular and mortality endpoints. In this article, we review landmark antihypertensive drug trials from the last two decades in patient populations composed, or including substantial proportions, of patients with type 2 diabetes. Several points emerge. Firstly, treatment effects can vary widely among different renal, cardiovascular and mortality endpoints. Secondly, combinations of antihypertensive drugs vary in their ability to prevent major renal and cardiovascular events, even if they produce similar reductions in blood pressure. Thirdly, simply adding further antihypertensive drugs may not improve outcomes, even if it produces further reductions in blood pressure. In most trials, a reduction in microalbuminuria was associated with evidence of renal protection, but further evidence is needed relating changes in proteinuria with cardiovascular risk. The study that aligns best with the current reappraisal of ESH guidelines, with regard to blood pressure goals, use of an adequate combination and simultaneously protecting the kidney and the cardiovascular system, is the ADVANCE study.

Key Words: *cardiovascular risk, hypertension, proteinuria, renal disease, renin–angiotensin–aldosterone system, type 2 diabetes*

Introduction

Co-existence of hypertension and diabetes mellitus substantially increases the risk of renal and other organ damage, and leads to a higher incidence of cardiac events and mortality. Chronic kidney disease (CKD) is prevalent in people with diabetes; a recent analysis of NHANES data found that 39.6% of people with diagnosed diabetes, 41.7% of those with undiagnosed diabetes and 17.7% of those with prediabetes had CKD (1). Renal dysfunction, including proteinuria and microalbuminuria, is predictive of cardiovascular events, and cardiovascular and all-cause mortality (2–5). A recent collaborative meta-analysis of general population cohorts involving more than 1 million participants has provided strong evidence of the direct relationship between renal dysfunction and cardiovascular risk. Estimated glomerular filtration rate < 60 ml/min/1.73 m^2 and an albumin-to-creatinine ratio ≥ 1.1 mg/mmol (≥ 10 mg/g) were both independent predictors of mortality risk in the general population. The two parameters increased mortality in a multiplicative fashion, without evidence of interaction. This study confirmed that 60 ml/min/1.73 m^2 for estimated glomerular filtration rate and the lower limit of high-normal albuminuria (1.1 mg/mmol [10 mg/g]) are adequate limits for risk assessment and for the definition and staging of CKD (6).

Diabetic patients are probably the most difficult hypertensive patients to treat, and, especially for those with renal dysfunction, combination therapy of several antihypertensive agents is usually required. There is evidence that blockers of the renin–angiotensin–aldosterone system (RAAS) may have specific renal protective properties, and such agents are preferred both for monotherapy and as components of combination therapy (7).

Antihypertensive treatments have been evaluated in many large, long-term randomized trials. However, several controversies remain regarding optimal antihypertensive therapy in diabetic patients. In this article, we attempt to review and evaluate recent landmark trials that have been instrumental in shaping current

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understanding and practice in the management of hypertension in type 2 diabetes. In doing so, we focus on several issues, including:

- whether benefits in terms of mortality and major morbidity depend solely on the attained level of blood pressure reduction with treatment;
- the possible adverse metabolic effects of some classes of antihypertensive drugs;
- the relationship between surrogate endpoints, especially renal endpoints, and 'hard' endpoints, particularly all-cause and cardiovascular mortality;
- the difficulties that the use of combinations of two or more drugs can raise for the design and interpretation of clinical trials.

End-of-millennium optimism

The closing years of the 20th century were marked by a series of trials highlighting the importance, and potentially large benefits, of effective hypertension treatment in patients with type 2 diabetes. One that has come to be regarded as a cornerstone trial is the UK Prospective Diabetes Study (UKPDS). The numbered series of papers arising directly from the study reached 81 in October 2008, but one of the most important was number 38, comparing the effects of tight blood pressure control on macro- and microvascular diabetic complications in patients with recently diagnosed type 2 diabetes (8). A total of 758 patients were randomized to a tight control group with a blood pressure target of $<150/85$ mmHg to be achieved using either captopril (400 patients) or atenolol (358 patients), with other agents added if required. A further 390 patients were allocated to less tight control (target $<180/105$ mmHg) using treatments other than beta-blockers and angiotensin-converting enzyme (ACE) inhibitors. After a median follow-up of 8.4 years, the blood pressures achieved in the two groups differed by less than their targets, being 144/82 and 154/87 mmHg in the tight and less tight control groups, respectively. However, the differences in outcome were striking, with a reduction of 32% in the risk of death related to diabetes in the tight control group, accompanied by reductions of 44% in stroke and 34% in all macrovascular diseases. By 6 years of follow-up, the risk of microalbuminuria (urinary albumin ≥ 50 mg/l) was reduced by 29%, and fewer patients showed deterioration in retinopathy in the tight control group. The study clearly showed the benefits of blood pressure control in preventing macro- and microvascular diabetic complications when using ACE inhibitors, and the authors concluded that management of blood pressure should have a high priority in the treatment of type 2 diabetes. Interestingly, 29% of patients in the tight control group required three or more antihypertensive treatments to achieve the blood pressure target. A subsequent analysis revealed no significant differences in any clinical endpoint between the captopril- and atenolol-based groups (9). Finally, a 10-year post-interventional follow-up study (10) showed that, after the end of the UKPDS trial, blood pressure levels rose in the tight control group and fell in the less tight control group, and the differences in risk between the groups decreased and became non-significant. Thus, optimal blood pressure control must be maintained to achieve lasting benefits.

Soon after the UKPDS came the Captopril Prevention Project (CAPPP), in which 10 985 patients were randomized to receive either the ACE inhibitor captopril or conventional treatment with diuretics and beta-blockers. During 6.1 years of follow-up, captopril and conventional treatment did not differ in preventing cardiovascular morbidity and mortality (11). However, in the relatively small subgroup of 572 patients with diabetes at baseline (4.9% of the overall patient sample), the primary composite endpoint of myocardial infarction, stroke and cardiovascular death was substantially lower in the captopril group (relative risk 0.59), and total mortality was also significantly reduced (relative risk 0.54). In this trial, the differences in outcome could not be explained by differences in blood pressure reductions: if anything, the achieved blood pressure levels were slightly lower with conventional treatment than with captopril in diabetic patients (12).

What these studies had in common was a clear demonstration of the very considerable benefits in terms of cardiovascular morbidity and mortality that could be achieved by antihypertensive therapies such as ACE inhibitors in patients with diabetes. However, they also gave an early indication of the controversies to come relating to specific benefits of different classes of antihypertensive drug and their combinations, and of the difficulties of clinical trial design when many effective treatments are available and optimum treatment for many patients will involve combinations of two or more drugs.

Turn of a new century – HOPE, PROGRESS and controversy

January 2000 saw the publication of the hugely influential Heart Outcomes Prevention Evaluation (HOPE) study (13). A total of 9297 high-risk patients with a history of vascular disease or diabetes plus one other cardiovascular risk factor were randomized to receive the ACE inhibitor ramipril or placebo for approximately 4.5 years. Study drugs were given on top of usual cardiovascular medications, except for RAAS inhibitors, which were not allowed unless required by patients' clinical condition during the study. Ramipril reduced the incidence of the primary outcome (the composite of myocardial infarction, stroke and cardiovascular

death) by 22%, cardiovascular death by 26% and all-cause death by 16%. An important finding was that the reduction in blood pressure with ramipril, relative to placebo, was small (approximately 3/2 mmHg), which the authors argued was too small to account for the observed benefits. A further result was that the incidence of new-onset diabetes during the study was markedly lower in the ramipril group, with a relative risk of 0.66. There soon followed a subgroup analysis in the 3577 patients with diabetes at baseline (14). The blood pressure reduction with ramipril was even smaller in this subgroup (2.4/1.0 mmHg), but the risk reductions tended to be slightly larger than in the full study population, with reductions in the primary outcome of 25%, cardiovascular death by 37%, and all-cause death by 24%. There was also a reduction in the incidence of overt nephropathy of 24%. A further analysis in patients with mild renal insufficiency (15) showed that such patients were at markedly increased risk of cardiovascular and all-cause mortality, and the relative risk reductions with ramipril were larger in patients with renal insufficiency (41% for both) than in those without (22% for cardiovascular and 10% for all-cause death).

The HOPE trial was soon followed by PROGRESS (16), which was primarily a study in secondary prevention of stroke, but which had important implications for subsequent trial design, especially regarding combination therapies. Patients ($n = 6105$) with history of stroke or transient ischaemic attack were randomized to active treatment with perindopril, with or without the addition of the diuretic indapamide, or placebo, and mean follow-up was 3.9 years. Overall, active treatment produced a reduction of 28% in stroke and 26% in major vascular events; the benefits were similar in hypertensive and non-hypertensive patients. Approximately 42% of patients were treated with perindopril alone and 58% with the perindopril + indapamide combination. Blood pressure was reduced by 5/3 mmHg by perindopril alone, and by 12/5 mmHg by the combination. Results in patients receiving the perindopril + indapamide combination were dramatic, with risk reductions of 43% in stroke and 40% in major vascular events. Subsequent analysis in the 761 patients with diabetes at baseline (17) indicated a non-significantly larger treatment effect in diabetic compared with non-diabetic patients, with risk reductions for stroke of 38% and 28%, respectively, and diabetic patients who received perindopril + indapamide showed a dramatic 46% reduction in stroke risk. The combination of perindopril and indapamide will feature again later in this review.

The results of these trials validated the benefits of ACE inhibitor therapy, a point reinforced by subsequent guidelines, and made a strong case for their use in control groups in later trials.

Angiotensin II receptor blockers and chlorthalidone: new challenges?

Two further studies from the early years of the 21st century must be mentioned. The LIFE study (18) compared treatment based on the angiotensin II receptor blocker (ARB), losartan, with one based on atenolol in a specific population of 9193 patients with left ventricular hypertrophy and hypertension (mean baseline blood pressure 174/98 mmHg), with a mean follow-up of 4.8 years. The majority of patients in both treatment groups also took hydrochlorothiazide, and many also took further antihypertensive drugs. Large but similar blood pressure reductions were seen in both groups, reaching 30/17 mmHg in the losartan group and 29/17 in the atenolol group. The risk of the primary endpoint, the composite of cardiovascular death, myocardial infarction and stroke, was reduced by 13% in the losartan group, with a significant decrease in risk of stroke of 25%, relative to atenolol-based treatment. Cardiovascular and all-cause mortality were not significantly different between the treatment groups. Interestingly, the incidence of new-onset diabetes was lower by 25% in the losartan group. In the subgroup of patients with diabetes at baseline, losartan treatment was associated with a reduction of 24% in the primary endpoint, and significant reductions of 37% in cardiovascular and 39% in all-cause mortality (19). In further sub-analyses in diabetic patients, both the level of albuminuria at baseline and the reduction in albuminuria during treatment were predictors of cardiovascular events. Albuminuria decreased more with losartan than with atenolol, and significant reductions in cardiovascular and all-cause mortality with losartan were found only among patients in the highest quartile of baseline microalbuminuria (20,21).

The results of the LIFE study have been the subject of considerable discussion, mainly centred on the use of atenolol as an active comparator. A systematic review concluded that the beta-blockers studied (principally atenolol) had no effect on coronary artery disease and all-cause mortality compared with placebo and had only a weak beneficial effect on stroke (22). Another review concluded that atenolol had no more effect on outcome than placebo on all-cause mortality, cardiovascular mortality or myocardial infarction, in spite of a substantial blood pressure lowering effect (23). The authors, who included one of the authors of the LIFE study, concluded that these results challenged the use of atenolol as a reference drug in outcome trials in hypertension. A further consideration is that there is evidence that beta-blockers, perhaps especially when used in combination with thiazide diuretics, can adversely affect glucose haemostasis (24,25). In the large prospective ARIC study, subjects with hypertension taking beta-blockers had a 28% higher risk of developing

diabetes than those with hypertension who were not taking any antihypertensive medication (26). Ironically, this is of similar magnitude to the 25% difference in incidence of new-onset diabetes between losartan and atenolol in the LIFE study (18).

The largest of all the hypertension mega-trials, the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT), also proved to be one of the most controversial (27), with numerous comments and criticisms, which prompted responses from the study authors (28,29). The study compared the thiazide diuretic, chlorthalidone, with the alpha-blocker doxazosin, amlodipine and lisinopril in 42 418 high-risk hypertensive patients. The doxazosin treatment arm was discontinued early, mainly because of a near-doubling of risk of heart failure, together with significantly increased risk of stroke and a combined cardiovascular disease endpoint (30,31). Interestingly, there were no differences between the doxazosin and chlorthalidone groups in either the primary study endpoint (a composite of fatal coronary heart disease and non-fatal myocardial infarction), or in all-cause mortality, despite a total of >2000 deaths in the two groups during a median of 3.3 years follow-up.

The main results of ALLHAT were that chlorthalidone did not differ from amlodipine and lisinopril in its effect on the primary endpoint, but was superior to the other agents for some secondary endpoints, including heart failure. Comments and criticisms have concerned many aspects of the trial design, including the use of atenolol as step 2 medication in all groups, resulting in some unusual combinations for many patients, including that of lisinopril and atenolol (28,29), and the low dose of lisinopril received by most patients (32). One of the main concerns, however, has been the observed increases in fasting glucose concentration and the incidence of new-onset diabetes in patients in the diuretic group (33–35). In patients without diabetes at baseline, fasting glucose levels at 2 years had increased by 8.5 mg/dl in the chlorthalidone group, compared with 3.5 mg/dl in the lisinopril group, and the odds ratio for new onset diabetes was 0.55 (95% CI 0.431–0.704, $P<0.001$) for lisinopril compared with diuretic (35).

Many other studies have indicated the risk of adverse metabolic effects associated with diuretic (and beta-blocker) treatment. In the ASCOT study in 14 120 non-diabetic patients (36), the risk of new-onset diabetes was substantially lower with an amlodipine ± perindopril regimen than with atenolol ± thiazide (hazard ratio 0.66, 95% CI 0.59–0.74). In a network meta-analysis of 22 trials, the odds ratios of new-onset diabetes with RAAS-inhibitors, relative to diuretics, were 0.57 for ARBs and 0.67 for ACE inhibitors (37). Several mechanisms for 'thiazide-induced dysglycaemia' (38) have been proposed, and hypokalaemia has been widely implicated. In non-diabetic patients in the SHEP study, the incidence rate of diabetes was more than doubled with chlorthalidone compared with placebo, and the risk was significantly reduced, but not abolished, by adjustment for change in serum potassium (39). Hypokalaemia may lead to diminished pancreatic β-cell response to glucose and reduced muscle perfusion, increased hepatic fat content, and vascular oxidative stress, all of which may impair glucose metabolism (38,40–44). Using thiazides in combination with an ACE inhibitor can minimize hypokalaemia and glucose intolerance (38), although this effect was not apparent when the ARB losartan was combined with hydrochlorothiazide in the STAR study (45).

RAAS inhibitors and nephropathy

Nephropathy has long been recognized as an important complication of diabetes, and diabetes and hypertension are the most common causes of CKD (46,47). Worsening renal disease carries a steeply increasing risk of cardiovascular death (48) (Figure 1), and the

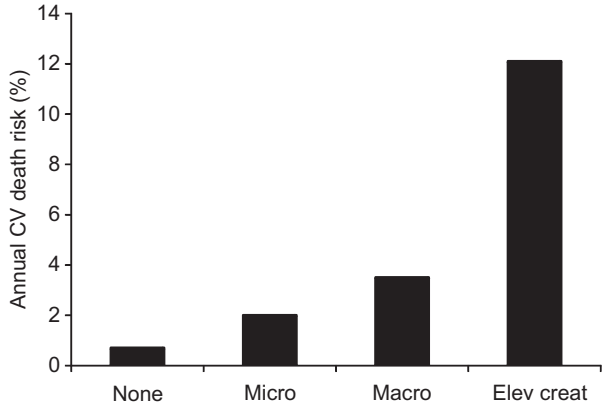

Figure 1. Annual risk of cardiovascular (CV) death in patients with type 2 diabetes mellitus and different degrees of nephropathy in the UK Prospective Diabetes Study (UKPDS). Micro, microalbuminuria; Macro, macroalbuminuria; Elev creat, elevated plasma creatinine or renal replacement therapy. Data from Adler et al. (48).

complex interactions between cardiovascular disease, CKD and diabetes are becoming more widely appreciated, if not fully understood (6,47,49). Blockade of the renin–angiotensin system is widely accepted as beneficial in terms of renal outcomes, and a series of meta-analyses have indicated that ACE inhibitors can prevent new-onset microalbuminuria, progression to macroalbuminuria, and reduce all-cause mortality in patients with diabetic nephropathy, and that ARBs have only renoprotective properties (50–54). During the last 10 years, there has been a series of placebo-controlled, randomized trials of ARBs in patient populations comprising or including patients with diabetes, with and without nephropathy. Characteristics of these trials are summarized in Table I, including the total number of deaths that occurred in each study, which is an indication of the power of the study to detect a mortality benefit of active treatment (55–64).

The approximate mortality rate in the placebo group of each trial is also given, as a measure of the risk status of the patient population. Full trial names are given in the footnote to Table I, and the main results are summarized in Table II.

The IDNT (55) and RENAAL (56) trials included patients with type 2 diabetes and nephropathy. In both trials, randomized treatments were given in addition to standard hypertensive therapy, which excluded ACE inhibitors, ARBs, and in the case of IDNT, calcium-channel blockers. In the IDNT trial, irbesartan treatment was associated with a 20% reduction, relative to placebo, in the primary renal endpoint (the composite of doubling of serum creatinine, end-stage renal disease, and all-cause death), mainly because of a 33% reduction in the doubling of serum creatinine (Table II). End-stage renal disease was reduced by 23%, but the difference just failed to reach significance ($P = 0.07$). Renal outcomes in the amlodipine group were similar to placebo. The RENAAL trial was stopped early on ethical grounds because of the exclusion of ACE inhibitors from permitted background therapies in the study design. During the mean 3.4 years of follow-up, losartan produced a significant 16% reduction in the primary renal endpoint (the same composite as in IDNT), with significant reductions in both doubling of serum creatinine and in end-stage renal disease (Table II). Losartan also led to an average reduction in the level of proteinuria (measured as urinary albumin to creatinine ratio; UACR) of 35% from baseline, whereas the ratio tended to increase in the placebo group ($P < 0.001$ for treatment effect). Despite the renal benefits in both trials, ARB treatment did not produce any substantial or significant improvement in the risk of all cardiovascular events or in all-cause or cardiovascular mortality. In the IDNT trial, irbesartan produced a significant reduction of 28% in heart failure, but no improvement in myocardial infarction, stroke or all-cause or cardiovascular death (which actually increased by 8%). This may be contrasted with the effect of amlodipine, which produced a significant reduction of 42% in myocardial infarction, and non-significant reductions in stroke and cardiovascular death of 35% and 21%, respectively, despite no discernible benefit in renal endpoints (65).

IRMA 2 (57) was a smaller study, which compared two doses of irbesartan with placebo in patients with type 2 diabetes and persistent microalbuminuria, who could receive other antihypertensive drugs apart from ARBs and ACE inhibitors. The primary efficacy endpoint was onset of overt nephropathy, defined as urinary albumin excretion rate > 200 μg/min and $\geq 30\%$ higher than at baseline, and this endpoint was reached by 30 patients in the placebo group, compared with 19 in the irbesartan 150-mg group and 10 in the 300mg group, corresponding to hazard ratios of 0.61 (NS) and 0.30 ($P < 0.001$), respectively. The level of urinary albumin excretion reduced by 38% in the irbesartan 300mg group compared with a reduction of 2% in the placebo group ($P < 0.001$). The number of deaths was eight in the irbesartan 300-mg group vs 5 in the placebo group.

In contrast to the previous three trials, patients in the TRANSCEND study (58,66) had either established cardiovascular disease or diabetes with end-organ damage but without macroalbuminuria or heart failure. Intolerance of ACE inhibitors was an inclusion requirement; other antihypertensive drugs were allowed, including non-study ARBs, although these were only taken by $< 10\%$ of patients. The primary renal endpoint was the composite of dialysis, renal transplantation, doubling of serum creatinine and death, and this occurred with similar incidence in the two groups. However, doubling of serum creatinine occurred significantly more frequently with telmisartan than with placebo (hazard ratio 1.59, $P = 0.031$), and significantly more patients experienced a reduction in estimated glomerular filtration rate with telmisartan. On the other hand, among patients with microalbuminuria at baseline, progression to macroalbuminuria was markedly reduced by 42% by telmisartan ($P = 0.018$). However, telmisartan had no significant effect on the main composite cardiovascular endpoint, or on all-cause or cardiovascular death. The authors concluded that ARBs offer no renal benefit in ACE-intolerant people at high vascular risk but without macroalbuminuria (66).

The next study in this category is a combined analysis of renal endpoints in the three DIRECT trials, which were designed primarily to evaluate the effect of candesartan on the incidence and progression of retinopathy in normoalbuminuric patients with type 1 or type 2 diabetes (59,67,68). The primary renal endpoint was development of microalbuminuria, with rate of change in urinary albumin excretion rate as a secondary endpoint. Similar numbers of patients in the candesartan and placebo

Table I. Characteristics of large randomized trials with renal endpoints including patients with diabetes mellitus.

Study	Patient characteristics	Treatments	Follow-up (years)	Baseline BP (mmHg)	BP difference vs control (mmHg)	Total deaths (approximate rate)[a]
Monotherapy vs placebo						
IDNT ($n=1715$) (55)	Type 2 DM + nephropathy	Irbesartan ($n=579$); placebo ($n=569$); amlodipine ($n=567$)	2.6	159/87	− 3.3	263 (55)
RENAAL ($n=1513$) (56)	Type 2 DM + nephropathy	Losartan ($n=751$); placebo ($n=762$)	3.4	153/82	− 2	313 (60)
IRMA 2 ($n=590$) (57)	Type 2 DM + persistent microalbuminuria	Irbesartan 150 mg ($n=195$); irbesartan 300 mg ($n=195$); placebo ($n=201$)	2.0	153/90	− 3	4 (2.5)
TRANSCEND ($n=5927$) (58)	Cardiovascular disease or DM with end-organ damage	Telmisartan ($n=2954$); placebo ($n=2972$)	4.7	141/82	− 4	713 (25)
DIRECT-Renal ($n=5231$) (59)	Type 1 and type 2 DM, normoalbuminuria	Candesartan ($n=2613$); placebo ($n=2618$)	4.7	118/73	− 3.3	99 (4)
ROADMAP ($n=4\,447$) (60)	Type 2 DM, normoalbuminuria + ≥ 1 cardiovascular risk factor	Olmesartan ($n=2232$); placebo ($n=2215$)	3.2	136/81	− 3.0;	41 (2.1);
Combination therapy						
ONTARGET ($n=25\,620$) (61)	Cardiovascular disease or DM with end-organ damage	Ramipril ($n=8576$); telmisartan ($n=8542$); ramipril + telmisartan ($n=8502$)	4.7	142/82	− 2.4; (combination vs ramipril)	3068 (25); (all groups)
ADVANCE ($n=11\,140$) (62)	Type 2 DM + cardiovascular disease or ≥ 1 risk factor	Perindopril + indapamide (N = 5569); Placebo ($n=5571$)	4.3	145/81	− 5.6	879 (18)
ACCOMPLISH ($n=11\,506$) (63)	Hypertension + cardiovascular disease or DM (in 60% of patients)	Benazepril + amlodipine ($n=5744$); Benazepril + hydrochlorothiazide; ($n=5762$)	3.0	145/80	− 1.1; (Ben + Am vs; Ben + Hyd)	498 (14); (both groups)
Comparison of blood pressure targets						
ACCORD BP ($n=4733$) (64)	Type 2 DM at high risk for cardiovascular events	Target BP < 120 mmHg systolic ($n=2362$); target BP < 140 mmHg systolic ($n=2371$);	5.0; (for mortality)	139/76	− 14.2	249 (10)

[a] Approximate rate given for placebo group unless stated, expressed as deaths per 1000 patient-years. Am: amlodipine; Ben: benazepril; BP: blood pressure (systolic if available); DM: diabetes mellitus; Hyd: hydrochlorothiazide.

Trial names: IDNT, Irbesartan Diabetic Nephropathy Trial; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study; IRMA 2, Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study; TRANSCEND, Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease; DIRECT, Diabetic Retinopathy Candesartan Trials; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention study; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; ADVANCE, Action in Diabetes and Vascular Disease, Preterax and Diamicron-MR Controlled Evaluation Trial; ACCOMPLISH, Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension; ACCORD BP, Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial.

Table II. Summary of results of large randomized trials with renal endpoints including patients with diabetes mellitus.

	Albuminuria		Renal endpoints			Cardiovascular		Mortality	
Study	New-onset	Progression	Primary endpoint or renal events	Doubling of serum creatinine	ESRD or dialysis	All events	Stroke	All-cause	Cardiovascular
Monotherapy vs placebo									
IDNT (55)									
Irbesartan vs placebo	–	–	−20% ($P=0.02$)	−33% ($P=0.003$)	−23% (NS)	−10% (NS)	+1% (NS)	−8% (NS)	+8% (NS)
Amlodipine vs placebo	–	–	+4% (NS)	+6% (NS)	0% (NS)	0% (NS)	−35% (NS)	−12% (NS)	−21% (NS)
RENAAL: Losartan vs placebo (56)	–	−35% in UACR ($P=0.001$)	−16% ($P=0.02$)	−25% ($P=0.006$)	−28% ($P=0.002$)	−10% (NS)	–	+2% (NS)	–
IRMA 2: Irbesartan 300 mg vs placebo (57)	–	−38% in urine albumin ($P<0.001$)	−70% ($P<0.001$)	–	–	–	–	Irbesartan: 8; placebo: 5	–
TRANSCEND: Telmisartan vs placebo (58)	-	−42% ($P=0.018$)	+10% (NS)	+59% ($P=0.031$)	−29% (NS)	−8% (NS)	−17% (NS)	+5% (NS)	+3% (NS)
DIRECT-Renal: Candesartan vs placebo (59)	−5% (NS) (primary renal endpoint)	–	Also a −5.5% change in UAER ($P=0.024$)	–	–	–	–	Candesartan: 51; placebo: 48	–
ROADMAP: Olmesartan vs placebo (60)	23% delay in time to onset ($P=0.01$) (primary endpoint)	–	–	0% (NS) (23 patients in each group)	Not observed in any patients	0% (NS)	–	+70% (NS)	+394% ($P=0.01$) (olmesartan: 15; placebo: 3)
Combination therapy									
ONTARGET (61)									
Telemisartan vs ramipril	−6% (NS)	−17% (NS)	0% (NS)	+11% (NS)	+7% (NS)	+1% (NS)	−9% (NS)	−2% (NS)	0% (NS)
Combination vs ramipril	−12% ($P=0.003$)	−24% ($P=0.019$)	+9% ($P=0.037$)	+20% (NS)	+33% (NS)	−1% (NS)	−7% (NS)	+7% (NS)	+4% (NS)
ADVANCE: Perindopril + indapamide vs placebo (62)	−21% ($P=0.0001$)	−22% ($P=0.001$)	−21% ($P<0.0001$)	+21% (NS)	+18% (NS)	−14% ($P=0.020$)	−6% (NS)	−14% ($P=0.025$)	−18% ($P=0.027$)
ACCOMPLISH: Benazepril + amlodipine vs benazepril + hydrochlorothiazide (63)	–	–	−48% ($P<0.0001$)	−49% ($P<0.0001$)	−47% (NS)	−17% ($P=0.002$)	−16% (NS)	−10% (NS)	−20% (NS)
Comparison of blood pressure targets									
ACCORD BP: Target < 120 mmHg vs target, < 140 mmHg systolic (64)	30.2% vs 32.3% (NS)	6.6% vs 8.7% ($P=0.009$)	–	24% vs 16% ($P<0.001$) (elevated serum creatinine only)	No significant difference	−13% (NS) (non-fatal MI only)	−41% ($P=0.01$)	+7% (NS)	+6% (NS)

MI, myocardial infarction; NS, not significant; UACR, urinary albumin-to-creatinine ratio; UAER, urinary albumin excretion rate. Full names of studies given in Table I.

groups developed microalbuminuria in each of the three studies, with a hazard ratio (candesartan vs placebo) of 0.95 in the combined analysis ($P = 0.60$). The annual rate of change in urinary albumin excretion rate was 5.5% lower with candesartan ($P = 0.024$); this corresponds to an absolute reduction of 0.11 μg/min, which the authors describe as modest and of uncertain clinical significance. However, it must be remembered that the study was not powered for a renal endpoint. The number of deaths was similar in the candesartan (51 deaths) and placebo (48 deaths) groups.

The most recent study in this category is the ROADMAP trial (60), in which olmesartan was compared with placebo in a group of 4447 normoalbuminuric patients with type 2 diabetes. The primary endpoint was new-onset microalbuminuria. Olmesartan delayed the time to onset of microalbuminuria by 23% ($P = 0.01$), and the number needed to treat for 5 years to prevent one case of new-onset microalbuminuria was 41 patients. Secondary end-points included cardiovascular events and all-cause and cardiovascular mortality. The total number of cardiovascular events was low and was the same with both treatments. However, there were 15 cases of death from cardiovascular causes in the olmesartan group compared with three cases in the placebo group ($P = 0.01$). The difference was attributable in part to a higher rate of cardiovascular death with olmesartan in patients with established coronary artery disease, especially those in the lowest quartile of systolic blood pressure on treatment and those with the largest reductions in blood pressure with treatment. The study authors concluded that these findings could be consistent with the "J-curve effect", but that a direct effect of olmesartan could not be ruled out.

The studies considered in this section suggest that treatment with ARBs can delay the onset of microalbuminuria and progression to macroalbuminuria, and reduce the incidence of manifestations of more severe renal disease such as doubling of serum creatinine and need for dialysis, although there were inconsistencies between different renal endpoints. However, none of the trials showed a significant benefit of ARBs on mortality. The lack of significant effect might be expected in trials with relatively small numbers of deaths, such as IRMA 2 and DIRECT. However, it is of more concern in those trials, which, because of their large size and/or the high-risk nature of their patients, involved substantial numbers of deaths, or, as in ROADMAP, showed an increased rate of cardiovascular death with ARB treatment. A recent analysis (69) of 16 randomized trials in predominantly hypertensive patients since 2000 indicated that only three trials (ASCOT-BPLA (70), ADVANCE (62) and HYVET (71)) showed a significant reduction in all-cause mortality. The successful treatments in these three studies were amlodipine (± perindopril), perindopril + indapamide, and indapamide (± perindopril), respectively. The other 13 studies, individually and when pooled, showed no significant mortality benefit (odds ratio 0.996 for the pooled analysis).

Specific combinations

Many hypertensive patients in clinical practice receive more than one antihypertensive drug, and the use of combination therapy is widely recommended in hypertension guidelines. Combinations may be especially important for patients with diabetes, for whom recommended blood pressure targets are challenging. It should be pointed out that in most large recent hypertension trials, the study drug is given on top of usual antihypertensive therapy, which is often left to the discretion of the investigator. Thus, most trials evaluate the efficacy of combinations of drugs, but the type and dose of the components other than the randomized study drug are not standardized. However, three large recent trials have explicitly studied specific combinations, with striking results.

In the very large ONTARGET trial (61,72), telmisartan and the combination of telmisartan and ramipril were compared with ramipril alone in patients with cardiovascular disease or diabetes with end-organ damage. There were no significant differences between the telmisartan and ramipril groups for any renal, cardiovascular or mortality endpoint (Table II). However, the comparison between the combination and ramipril alone revealed important differences.

The combination was more effective than ramipril alone in preventing new-onset microalbuminuria and progression of pre-existing microalbuminuria, with hazard ratios of 0.88 ($P = 0.003$) and 0.76 ($P = 0.019$), respectively. On the other hand, the primary renal endpoint, the composite of doubling of serum creatinine, dialysis or death, occurred significantly more frequently with the combination than with ramipril (hazard ratio 1.09, $P = 0.037$); each component was numerically more frequent with the combination, by 20%, 33% and 7%, respectively. Declines in estimated glomerular filtration rate were greater with the combination than with ramipril ($P < 0.0001$). Rates of cardiovascular endpoints and mortality were similar in the combination and ramipril groups. Renal abnormalities were reported as adverse events in significantly more patients in the combination group than with ramipril (relative risk 1.33, $P < 0.0001$), and more patients stopped medication because of renal abnormalities with the combination than with ramipril (relative risk 1.58, $P < 0.005$). Thus, the addition of telmisartan to ramipril reduced the incidence of proteinuria, but caused a more rapid decline in glomerular filtration rate, increased the incidence of major renal events, and showed no benefit in terms of cardiovascular events or mortality. This may be

one of the reasons why guidelines do not recommend this combination.

The ADVANCE trial is the largest trial performed in diabetics, involving 11 140 patients. It compared a fixed-dose combination of perindopril and the original diuretic indapamide with placebo in patients with type 2 diabetes and a history of major cardiovascular disease or at least one other cardiovascular risk factor (62,73). Combination therapy reduced the composite renal endpoint (new-onset microalbuminuria, new-onset nephropathy, doubling of serum creatinine or end-stage renal disease) by 21% (hazard ratio 0.79, $P < 0.0001$). There were also significant reductions in new-onset microalbuminuria (21%) and progression from microalbuminuria to macroalbuminuria (31%). The number needed to treat for 5 years to prevent one case of new-onset microalbuminuria in ADVANCE was 16 patients, which may be contrasted with the corresponding figure of 41 patients with ARB treatment in the ROADMAP trial (60). Later-stage renal events were infrequent in the ADVANCE population, and end-stage renal disease occurred with similar frequency in the combination and placebo groups. However, new or worsening nephropathy was reduced in patients with an UACR ≥ 30 (74). In contrast to the trials of ARBs described in the previous section, the renal benefits of the perindopril + indapamide combination were accompanied by significant reductions in all-cause mortality (by 14%, $P = 0.025$), cardiovascular death (by 18%, $P = 0.027$) and coronary events (by 14%, $P = 0.020$). At least three further features of the ADVANCE trial are notable. Firstly, almost all other antihypertensive treatments were allowed (including RAAS-inhibitors in 73% of patients of the control group, a first in these trials), except that thiazide diuretics were not permitted. The effectiveness of the permitted treatments was illustrated by the fact that regression of albuminuria by at least one stage was observed in 50.2% of patients in the placebo group; nonetheless, active treatment provided a further benefit of 16% in the incidence of regression ($P = 0.0017$). Secondly, significant reductions in renal events were seen in all subgroups of patients defined by baseline blood pressure, including those with starting blood pressure below 125/75 mmHg. Indeed, the lowest risk for renal events was observed in patients with achieved blood pressure levels below 110 mmHg systolic or 65 mmHg diastolic. Thirdly, a recent analysis has shown that the relative risk of all-cause mortality was reduced to a similar extent in patients with or without nephropathy, and whatever their CKD stage at baseline (74). One issue not resolved by ADVANCE was whether the observed benefits were independent of blood pressure reduction, because the blood pressure achieved was lower in the active treatment group by an average of 5.6 mmHg systolic and 2.2 mmHg diastolic. However, since the majority of diabetic patients with hypertension in clinical practice do not reach their target blood pressure (75), the greater antihypertensive efficacy of the perindopril + indapamide combination could be regarded as an additional positive result.

The third trial in this group is ACCOMPLISH (63,76), which compared two fixed-dose combinations – benazepril + amlodipine and benazepril + hydrochlorothiazide – in 11 506 patients with hypertension and a history of cardiovascular disease or diabetes; approximately 60% (6946) of randomized patients had diabetes. The primary endpoint was the composite of cardiovascular events and cardiovascular death, and the trial was halted prematurely because of a significant reduction in this endpoint in the benazepril + amlodipine group (hazard ratio 0.80, $P < 0.001$). There was a significant reduction in the composite of all cardiovascular events (17%, $P = 0.002$), but the reductions in all-cause death (10%), cardiovascular death (20%) and stroke (16%) did not reach significance. The primary renal endpoint, the composite of doubling of serum creatinine and end-stage renal disease, was almost halved in the benazepril + amlodipine group (hazard ratio 0.52, $P < 0.0001$), related mainly to a 49% reduction in doubling of serum creatinine ($P < 0.0001$). As in the ADVANCE trial, dialysis was infrequent, occurring in seven patients in the benazepril + amlodipine group and 13 patients in the benazepril + hydrochlorothiazide group (NS). Despite the marked reduction in later-stage renal events with benazepril + amlodipine, the proportion of patients with baseline microalbuminuria who regressed to normoalbuminuria was substantially lower in this group (41.7%) than with benazepril + hydrochlorothiazide (68.3%, $P = 0.0016$). The systolic blood pressure level in the two treatment groups differed by less than 1 mmHg. In the diabetic subgroup (77), the incidence of the primary endpoint was also significantly lower in the benazapil + amlodipine group with a hazard ratio of 0.79, similar to that in non-diabetic patients (hazard ratio 0.82). The renal outcome results from the ACCOMPLISH study confirm the need for future hypertension trials to consider cardiovascular and renal outcomes jointly (76), and indicate that the mechanisms that facilitate the progression of cardiovascular disease have similarities to those that lead to the progression of renal disease.

Intensive therapy – more is not always better

The final trial that we consider was of very different design. The recent ACCORD study (64) in 4733 patients with type 2 diabetes did not compare specific drugs or combinations, but rather evaluated the benefit of intensive blood pressure lowering to a target of < 120 mmHg systolic compared with standard therapy with a target of < 140 mmHg. In this trial, the drug regimens used in both groups were at the discretion of the individual investigators, and

treatments were administered in open-label fashion. Essentially, drugs from all the major antihypertensive drug classes were used more frequently in the intensive treatment group (Figure 2). The mean numbers of antihypertensive drugs taken at 1 year was 3.4 in the intensive group and 2.1 in the standard therapy group, and by the end of the study 41% of patients in the intensive group were taking drugs from ≥ 4 classes (including RAAS inhibitors). Achieved blood pressures averaged 119/64 in the intensive group and 134/71 with standard therapy. There was a significant reduction in the occurrence of macroalbuminuria in the intensive group (6.6% vs 8.7%, $P = 0.009$), but elevated serum creatinine was reported more frequently with intensive (23.8%) compared with standard therapy (15.5%, $P < 0.001$). There was no benefit of intensive therapy in the primary endpoint (the composite of myocardial infarction, stroke or cardiovascular death), or in all-cause and cardiovascular mortality, or in the frequency of end-stage renal disease or the need for dialysis. On the other hand, there was a marked reduction in the frequency of stroke with intensive therapy (hazard ratio 0.59, $P = 0.01$). A further consideration is that the rate of serious adverse events was significantly higher with intensive therapy. Although there was variation between different endpoints, intensive therapy showed little evidence of benefit, and some signals of possible harm.

At least four points emerge with some clarity from this disparate group of studies of combination therapy and blood pressure targets. Firstly, the effects of treatment can vary widely among different endpoints. Secondly, combinations of antihypertensive drugs vary widely in their ability to prevent major renal and cardiovascular events, even if they produce similar reductions in blood pressure. Thirdly, the addition of further antihypertensive drugs in patients already taking one or more antihypertensive drugs may not improve renal and mortality outcomes, even if it produces a further reduction in blood pressure. Intensive blood pressure lowering to < 120 mmHg systolic using 'ad hoc' combinations and doses in the ACCORD trial did not reduce major renal events or mortality compared with standard therapy. Finally, the only treatment providing primary and secondary prevention of renal events together with significant benefits in terms of all-cause and cardiovascular mortality, relative to a control group including RAAS inhibitors, was the perindopril + indapamide combination in the ADVANCE study. This trial can be considered as the study that fits best with the current reappraisal of the ESH guidelines with regard to the achievement of BP objectives, use of an adequate combination and achieving simultaneous protection of the kidney and the cardiovascular system (78).

Conclusions

Overall, the results of the trials reviewed here support the concept that aggressive blood pressure lowering is a vital element in the management of patients with type 2 diabetes, especially if they have evidence of renal involvement. However, it is clear that antihypertensive drugs and combinations differ widely in their effects, particularly regarding their capacity to reduce mortality, and the differences may be especially important in diabetic patients. Agents such as beta-blockers and thiazide diuretics may have adverse metabolic effects and may not be ideal choices in patients with, or at high risk of developing, diabetes. The near-universal use of more than one drug class to achieve target blood pressure in diabetic patients has important implications for clinical trial design and interpretation. Beneficial and adverse effects of one drug may be accentuated or minimized by concomitant therapies, but the types and doses of background therapies are often not standardized in trials. Explicit evaluation of fixed-dose combinations is in its infancy, but has

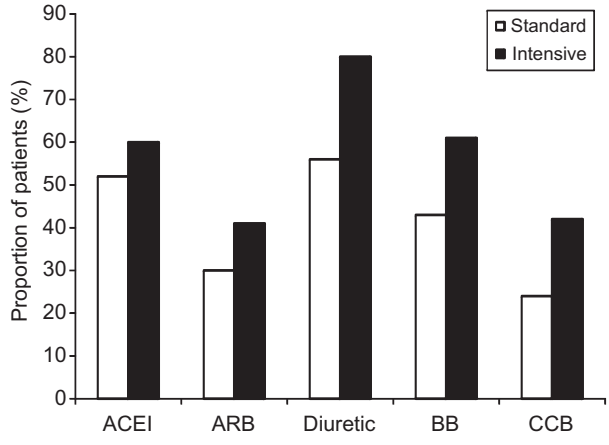

Figure 2. Main classes of antihypertensive drugs prescribed at the last study visit in patients in the intensive and standard treatment groups in the ACCORD trial. Alpha blockers, reserpine and other antihypertensive were also prescribed in $< 25\%$ of patients in either group. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; BB, beta-blocker; CCB, calcium channel blocker. Data from Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial (ACCORD) Study Group (64).

already highlighted large differences in their effect on outcome, even when their effect on blood pressure is the same. Finally, the strategy of simply adding additional drugs to patients already receiving two or more in an effort to drive blood pressure to ever lower levels may be counterproductive.

A lack of concordance among different renal endpoints and between renal and mortality endpoints emerged clearly from this review, and is consistent with concerns expressed over the use of proteinuria as a surrogate for kidney disease progression (79,80). Rates of end-stage renal disease or dialysis may also be of limited value, since these outcomes are relatively infrequent, and patients with macroalbuminuria are more likely to die than to progress to renal failure (48). Ultimately, all-cause and cardiovascular mortality are the most reliable trial endpoints, and so far only few and limited subgroups of trials have demonstrated simultaneous reduction of microalbuminuria and mortality in diabetic patients.

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REVIEW ARTICLE

A review of renal, cardiovascular and mortality endpoints in antihypertensive trials in diabetic patients

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Abstract

Renal disease is highly prevalent in people with type 2 diabetes, and co-existence with hypertension increases the risk of cardiac events and mortality. Despite many large randomized trials, controversies remain regarding optimal antihypertensive therapy in diabetic patients, including whether some classes of antihypertensive drugs have specific renal protective properties, and the relationships between renal, cardiovascular and mortality endpoints. In this article, we review landmark antihypertensive drug trials from the last two decades in patient populations composed, or including substantial proportions, of patients with type 2 diabetes. Several points emerge. Firstly, treatment effects can vary widely among different renal, cardiovascular and mortality endpoints. Secondly, combinations of antihypertensive drugs vary in their ability to prevent major renal and cardiovascular events, even if they produce similar reductions in blood pressure. Thirdly, simply adding further antihypertensive drugs may not improve outcomes, even if it produces further reductions in blood pressure. In most trials, a reduction in microalbuminuria was associated with evidence of renal protection, but further evidence is needed relating changes in proteinuria with cardiovascular risk. The study that aligns best with the current reappraisal of ESH guidelines, with regard to blood pressure goals, use of an adequate combination and simultaneously protecting the kidney and the cardiovascular system, is the ADVANCE study.

Key Words: *cardiovascular risk, hypertension, proteinuria, renal disease, renin–angiotensin–aldosterone system, type 2 diabetes*

Introduction

Co-existence of hypertension and diabetes mellitus substantially increases the risk of renal and other organ damage, and leads to a higher incidence of cardiac events and mortality. Chronic kidney disease (CKD) is prevalent in people with diabetes; a recent analysis of NHANES data found that 39.6% of people with diagnosed diabetes, 41.7% of those with undiagnosed diabetes and 17.7% of those with prediabetes had CKD (1). Renal dysfunction, including proteinuria and microalbuminuria, is predictive of cardiovascular events, and cardiovascular and all-cause mortality (2–5). A recent collaborative meta-analysis of general population cohorts involving more than 1 million participants has provided strong evidence of the direct relationship between renal dysfunction and cardiovascular risk. Estimated glomerular filtration rate < 60 ml/min/1.73 m^2 and an albumin-to-creatinine ratio ≥ 1.1 mg/mmol (≥ 10 mg/g) were both independent predictors of mortality risk in the general population. The two parameters increased mortality in a multiplicative fashion, without evidence of interaction. This study confirmed that 60 ml/min/1.73 m^2 for estimated glomerular filtration rate and the lower limit of high-normal albuminuria (1.1 mg/mmol [10 mg/g]) are adequate limits for risk assessment and for the definition and staging of CKD (6).

Diabetic patients are probably the most difficult hypertensive patients to treat, and, especially for those with renal dysfunction, combination therapy of several antihypertensive agents is usually required. There is evidence that blockers of the renin–angiotensin–aldosterone system (RAAS) may have specific renal protective properties, and such agents are preferred both for monotherapy and as components of combination therapy (7).

Antihypertensive treatments have been evaluated in many large, long-term randomized trials. However, several controversies remain regarding optimal antihypertensive therapy in diabetic patients. In this article, we attempt to review and evaluate recent landmark trials that have been instrumental in shaping current

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understanding and practice in the management of hypertension in type 2 diabetes. In doing so, we focus on several issues, including:

- whether benefits in terms of mortality and major morbidity depend solely on the attained level of blood pressure reduction with treatment;
- the possible adverse metabolic effects of some classes of antihypertensive drugs;
- the relationship between surrogate endpoints, especially renal endpoints, and 'hard' endpoints, particularly all-cause and cardiovascular mortality;
- the difficulties that the use of combinations of two or more drugs can raise for the design and interpretation of clinical trials.

End-of-millennium optimism

The closing years of the 20th century were marked by a series of trials highlighting the importance, and potentially large benefits, of effective hypertension treatment in patients with type 2 diabetes. One that has come to be regarded as a cornerstone trial is the UK Prospective Diabetes Study (UKPDS). The numbered series of papers arising directly from the study reached 81 in October 2008, but one of the most important was number 38, comparing the effects of tight blood pressure control on macro- and microvascular diabetic complications in patients with recently diagnosed type 2 diabetes (8). A total of 758 patients were randomized to a tight control group with a blood pressure target of $<150/85$ mmHg to be achieved using either captopril (400 patients) or atenolol (358 patients), with other agents added if required. A further 390 patients were allocated to less tight control (target $<180/105$ mmHg) using treatments other than beta-blockers and angiotensin-converting enzyme (ACE) inhibitors. After a median follow-up of 8.4 years, the blood pressures achieved in the two groups differed by less than their targets, being 144/82 and 154/87 mmHg in the tight and less tight control groups, respectively. However, the differences in outcome were striking, with a reduction of 32% in the risk of death related to diabetes in the tight control group, accompanied by reductions of 44% in stroke and 34% in all macrovascular diseases. By 6 years of follow-up, the risk of microalbuminuria (urinary albumin ≥ 50 mg/l) was reduced by 29%, and fewer patients showed deterioration in retinopathy in the tight control group. The study clearly showed the benefits of blood pressure control in preventing macro- and microvascular diabetic complications when using ACE inhibitors, and the authors concluded that management of blood pressure should have a high priority in the treatment of type 2 diabetes. Interestingly, 29% of patients in the tight control group required three or more antihypertensive treatments to achieve the blood pressure target. A subsequent analysis revealed no significant differences in any clinical endpoint between the captopril- and atenolol-based groups (9). Finally, a 10-year post-interventional follow-up study (10) showed that, after the end of the UKPDS trial, blood pressure levels rose in the tight control group and fell in the less tight control group, and the differences in risk between the groups decreased and became non-significant. Thus, optimal blood pressure control must be maintained to achieve lasting benefits.

Soon after the UKPDS came the Captopril Prevention Project (CAPPP), in which 10 985 patients were randomized to receive either the ACE inhibitor captopril or conventional treatment with diuretics and beta-blockers. During 6.1 years of follow-up, captopril and conventional treatment did not differ in preventing cardiovascular morbidity and mortality (11). However, in the relatively small subgroup of 572 patients with diabetes at baseline (4.9% of the overall patient sample), the primary composite endpoint of myocardial infarction, stroke and cardiovascular death was substantially lower in the captopril group (relative risk 0.59), and total mortality was also significantly reduced (relative risk 0.54). In this trial, the differences in outcome could not be explained by differences in blood pressure reductions: if anything, the achieved blood pressure levels were slightly lower with conventional treatment than with captopril in diabetic patients (12).

What these studies had in common was a clear demonstration of the very considerable benefits in terms of cardiovascular morbidity and mortality that could be achieved by antihypertensive therapies such as ACE inhibitors in patients with diabetes. However, they also gave an early indication of the controversies to come relating to specific benefits of different classes of antihypertensive drug and their combinations, and of the difficulties of clinical trial design when many effective treatments are available and optimum treatment for many patients will involve combinations of two or more drugs.

Turn of a new century – HOPE, PROGRESS and controversy

January 2000 saw the publication of the hugely influential Heart Outcomes Prevention Evaluation (HOPE) study (13). A total of 9297 high-risk patients with a history of vascular disease or diabetes plus one other cardiovascular risk factor were randomized to receive the ACE inhibitor ramipril or placebo for approximately 4.5 years. Study drugs were given on top of usual cardiovascular medications, except for RAAS inhibitors, which were not allowed unless required by patients' clinical condition during the study. Ramipril reduced the incidence of the primary outcome (the composite of myocardial infarction, stroke and cardiovascular

death) by 22%, cardiovascular death by 26% and all-cause death by 16%. An important finding was that the reduction in blood pressure with ramipril, relative to placebo, was small (approximately 3/2 mmHg), which the authors argued was too small to account for the observed benefits. A further result was that the incidence of new-onset diabetes during the study was markedly lower in the ramipril group, with a relative risk of 0.66. There soon followed a subgroup analysis in the 3577 patients with diabetes at baseline (14). The blood pressure reduction with ramipril was even smaller in this subgroup (2.4/1.0 mmHg), but the risk reductions tended to be slightly larger than in the full study population, with reductions in the primary outcome of 25%, cardiovascular death by 37%, and all-cause death by 24%. There was also a reduction in the incidence of overt nephropathy of 24%. A further analysis in patients with mild renal insufficiency (15) showed that such patients were at markedly increased risk of cardiovascular and all-cause mortality, and the relative risk reductions with ramipril were larger in patients with renal insufficiency (41% for both) than in those without (22% for cardiovascular and 10% for all-cause death).

The HOPE trial was soon followed by PROGRESS (16), which was primarily a study in secondary prevention of stroke, but which had important implications for subsequent trial design, especially regarding combination therapies. Patients ($n = 6105$) with history of stroke or transient ischaemic attack were randomized to active treatment with perindopril, with or without the addition of the diuretic indapamide, or placebo, and mean follow-up was 3.9 years. Overall, active treatment produced a reduction of 28% in stroke and 26% in major vascular events; the benefits were similar in hypertensive and non-hypertensive patients. Approximately 42% of patients were treated with perindopril alone and 58% with the perindopril + indapamide combination. Blood pressure was reduced by 5/3 mmHg by perindopril alone, and by 12/5 mmHg by the combination. Results in patients receiving the perindopril + indapamide combination were dramatic, with risk reductions of 43% in stroke and 40% in major vascular events. Subsequent analysis in the 761 patients with diabetes at baseline (17) indicated a non-significantly larger treatment effect in diabetic compared with non-diabetic patients, with risk reductions for stroke of 38% and 28%, respectively, and diabetic patients who received perindopril + indapamide showed a dramatic 46% reduction in stroke risk. The combination of perindopril and indapamide will feature again later in this review.

The results of these trials validated the benefits of ACE inhibitor therapy, a point reinforced by subsequent guidelines, and made a strong case for their use in control groups in later trials.

Angiotensin II receptor blockers and chlorthalidone: new challenges?

Two further studies from the early years of the 21st century must be mentioned. The LIFE study (18) compared treatment based on the angiotensin II receptor blocker (ARB), losartan, with one based on atenolol in a specific population of 9193 patients with left ventricular hypertrophy and hypertension (mean baseline blood pressure 174/98 mmHg), with a mean follow-up of 4.8 years. The majority of patients in both treatment groups also took hydrochlorothiazide, and many also took further antihypertensive drugs. Large but similar blood pressure reductions were seen in both groups, reaching 30/17 mmHg in the losartan group and 29/17 in the atenolol group. The risk of the primary endpoint, the composite of cardiovascular death, myocardial infarction and stroke, was reduced by 13% in the losartan group, with a significant decrease in risk of stroke of 25%, relative to atenolol-based treatment. Cardiovascular and all-cause mortality were not significantly different between the treatment groups. Interestingly, the incidence of new-onset diabetes was lower by 25% in the losartan group. In the subgroup of patients with diabetes at baseline, losartan treatment was associated with a reduction of 24% in the primary endpoint, and significant reductions of 37% in cardiovascular and 39% in all-cause mortality (19). In further sub-analyses in diabetic patients, both the level of albuminuria at baseline and the reduction in albuminuria during treatment were predictors of cardiovascular events. Albuminuria decreased more with losartan than with atenolol, and significant reductions in cardiovascular and all-cause mortality with losartan were found only among patients in the highest quartile of baseline microalbuminuria (20,21).

The results of the LIFE study have been the subject of considerable discussion, mainly centred on the use of atenolol as an active comparator. A systematic review concluded that the beta-blockers studied (principally atenolol) had no effect on coronary artery disease and all-cause mortality compared with placebo and had only a weak beneficial effect on stroke (22). Another review concluded that atenolol had no more effect on outcome than placebo on all-cause mortality, cardiovascular mortality or myocardial infarction, in spite of a substantial blood pressure lowering effect (23). The authors, who included one of the authors of the LIFE study, concluded that these results challenged the use of atenolol as a reference drug in outcome trials in hypertension. A further consideration is that there is evidence that beta-blockers, perhaps especially when used in combination with thiazide diuretics, can adversely affect glucose haemostasis (24,25). In the large prospective ARIC study, subjects with hypertension taking beta-blockers had a 28% higher risk of developing

diabetes than those with hypertension who were not taking any antihypertensive medication (26). Ironically, this is of similar magnitude to the 25% difference in incidence of new-onset diabetes between losartan and atenolol in the LIFE study (18).

The largest of all the hypertension mega-trials, the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT), also proved to be one of the most controversial (27), with numerous comments and criticisms, which prompted responses from the study authors (28,29). The study compared the thiazide diuretic, chlorthalidone, with the alpha-blocker doxazosin, amlodipine and lisinopril in 42 418 high-risk hypertensive patients. The doxazosin treatment arm was discontinued early, mainly because of a near-doubling of risk of heart failure, together with significantly increased risk of stroke and a combined cardiovascular disease endpoint (30,31). Interestingly, there were no differences between the doxazosin and chlorthalidone groups in either the primary study endpoint (a composite of fatal coronary heart disease and non-fatal myocardial infarction), or in all-cause mortality, despite a total of >2000 deaths in the two groups during a median of 3.3 years follow-up.

The main results of ALLHAT were that chlorthalidone did not differ from amlodipine and lisinopril in its effect on the primary endpoint, but was superior to the other agents for some secondary endpoints, including heart failure. Comments and criticisms have concerned many aspects of the trial design, including the use of atenolol as step 2 medication in all groups, resulting in some unusual combinations for many patients, including that of lisinopril and atenolol (28,29), and the low dose of lisinopril received by most patients (32). One of the main concerns, however, has been the observed increases in fasting glucose concentration and the incidence of new-onset diabetes in patients in the diuretic group (33–35). In patients without diabetes at baseline, fasting glucose levels at 2 years had increased by 8.5 mg/dl in the chlorthalidone group, compared with 3.5 mg/dl in the lisinopril group, and the odds ratio for new onset diabetes was 0.55 (95% CI 0.431–0.704, $P<0.001$) for lisinopril compared with diuretic (35).

Many other studies have indicated the risk of adverse metabolic effects associated with diuretic (and beta-blocker) treatment. In the ASCOT study in 14 120 non-diabetic patients (36), the risk of new-onset diabetes was substantially lower with an amlodipine ± perindopril regimen than with atenolol ± thiazide (hazard ratio 0.66, 95% CI 0.59–0.74). In a network meta-analysis of 22 trials, the odds ratios of new-onset diabetes with RAAS-inhibitors, relative to diuretics, were 0.57 for ARBs and 0.67 for ACE inhibitors (37). Several mechanisms for 'thiazide-induced dysglycaemia' (38) have been proposed, and hypokalaemia has been widely implicated. In non-diabetic patients in the SHEP study, the incidence rate of diabetes was more than doubled with chlorthalidone compared with placebo, and the risk was significantly reduced, but not abolished, by adjustment for change in serum potassium (39). Hypokalaemia may lead to diminished pancreatic β-cell response to glucose and reduced muscle perfusion, increased hepatic fat content, and vascular oxidative stress, all of which may impair glucose metabolism (38,40–44). Using thiazides in combination with an ACE inhibitor can minimize hypokalaemia and glucose intolerance (38), although this effect was not apparent when the ARB losartan was combined with hydrochlorothiazide in the STAR study (45).

RAAS inhibitors and nephropathy

Nephropathy has long been recognized as an important complication of diabetes, and diabetes and hypertension are the most common causes of CKD (46,47). Worsening renal disease carries a steeply increasing risk of cardiovascular death (48) (Figure 1), and the

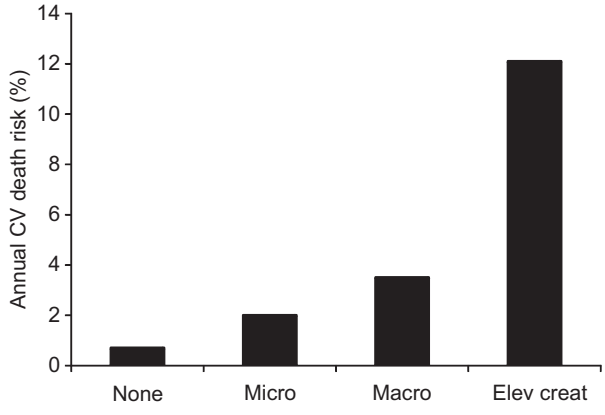

Figure 1. Annual risk of cardiovascular (CV) death in patients with type 2 diabetes mellitus and different degrees of nephropathy in the UK Prospective Diabetes Study (UKPDS). Micro, microalbuminuria; Macro, macroalbuminuria; Elev creat, elevated plasma creatinine or renal replacement therapy. Data from Adler et al. (48).

complex interactions between cardiovascular disease, CKD and diabetes are becoming more widely appreciated, if not fully understood (6,47,49). Blockade of the renin–angiotensin system is widely accepted as beneficial in terms of renal outcomes, and a series of meta-analyses have indicated that ACE inhibitors can prevent new-onset microalbuminuria, progression to macroalbuminuria, and reduce all-cause mortality in patients with diabetic nephropathy, and that ARBs have only renoprotective properties (50–54). During the last 10 years, there has been a series of placebo-controlled, randomized trials of ARBs in patient populations comprising or including patients with diabetes, with and without nephropathy. Characteristics of these trials are summarized in Table I, including the total number of deaths that occurred in each study, which is an indication of the power of the study to detect a mortality benefit of active treatment (55–64).

The approximate mortality rate in the placebo group of each trial is also given, as a measure of the risk status of the patient population. Full trial names are given in the footnote to Table I, and the main results are summarized in Table II.

The IDNT (55) and RENAAL (56) trials included patients with type 2 diabetes and nephropathy. In both trials, randomized treatments were given in addition to standard hypertensive therapy, which excluded ACE inhibitors, ARBs, and in the case of IDNT, calcium-channel blockers. In the IDNT trial, irbesartan treatment was associated with a 20% reduction, relative to placebo, in the primary renal endpoint (the composite of doubling of serum creatinine, end-stage renal disease, and all-cause death), mainly because of a 33% reduction in the doubling of serum creatinine (Table II). End-stage renal disease was reduced by 23%, but the difference just failed to reach significance ($P = 0.07$). Renal outcomes in the amlodipine group were similar to placebo. The RENAAL trial was stopped early on ethical grounds because of the exclusion of ACE inhibitors from permitted background therapies in the study design. During the mean 3.4 years of follow-up, losartan produced a significant 16% reduction in the primary renal endpoint (the same composite as in IDNT), with significant reductions in both doubling of serum creatinine and in end-stage renal disease (Table II). Losartan also led to an average reduction in the level of proteinuria (measured as urinary albumin to creatinine ratio; UACR) of 35% from baseline, whereas the ratio tended to increase in the placebo group ($P < 0.001$ for treatment effect). Despite the renal benefits in both trials, ARB treatment did not produce any substantial or significant improvement in the risk of all cardiovascular events or in all-cause or cardiovascular mortality. In the IDNT trial, irbesartan produced a significant reduction of 28% in heart failure, but no improvement in myocardial infarction, stroke or all-cause or cardiovascular death (which actually increased by 8%). This may be contrasted with the effect of amlodipine, which produced a significant reduction of 42% in myocardial infarction, and non-significant reductions in stroke and cardiovascular death of 35% and 21%, respectively, despite no discernible benefit in renal endpoints (65).

IRMA 2 (57) was a smaller study, which compared two doses of irbesartan with placebo in patients with type 2 diabetes and persistent microalbuminuria, who could receive other antihypertensive drugs apart from ARBs and ACE inhibitors. The primary efficacy endpoint was onset of overt nephropathy, defined as urinary albumin excretion rate > 200 μg/min and $\geq 30\%$ higher than at baseline, and this endpoint was reached by 30 patients in the placebo group, compared with 19 in the irbesartan 150-mg group and 10 in the 300mg group, corresponding to hazard ratios of 0.61 (NS) and 0.30 ($P < 0.001$), respectively. The level of urinary albumin excretion reduced by 38% in the irbesartan 300mg group compared with a reduction of 2% in the placebo group ($P < 0.001$). The number of deaths was eight in the irbesartan 300-mg group vs 5 in the placebo group.

In contrast to the previous three trials, patients in the TRANSCEND study (58,66) had either established cardiovascular disease or diabetes with end-organ damage but without macroalbuminuria or heart failure. Intolerance of ACE inhibitors was an inclusion requirement; other antihypertensive drugs were allowed, including non-study ARBs, although these were only taken by $< 10\%$ of patients. The primary renal endpoint was the composite of dialysis, renal transplantation, doubling of serum creatinine and death, and this occurred with similar incidence in the two groups. However, doubling of serum creatinine occurred significantly more frequently with telmisartan than with placebo (hazard ratio 1.59, $P = 0.031$), and significantly more patients experienced a reduction in estimated glomerular filtration rate with telmisartan. On the other hand, among patients with microalbuminuria at baseline, progression to macroalbuminuria was markedly reduced by 42% by telmisartan ($P = 0.018$). However, telmisartan had no significant effect on the main composite cardiovascular endpoint, or on all-cause or cardiovascular death. The authors concluded that ARBs offer no renal benefit in ACE-intolerant people at high vascular risk but without macroalbuminuria (66).

The next study in this category is a combined analysis of renal endpoints in the three DIRECT trials, which were designed primarily to evaluate the effect of candesartan on the incidence and progression of retinopathy in normoalbuminuric patients with type 1 or type 2 diabetes (59,67,68). The primary renal endpoint was development of microalbuminuria, with rate of change in urinary albumin excretion rate as a secondary endpoint. Similar numbers of patients in the candesartan and placebo

Table I. Characteristics of large randomized trials with renal endpoints including patients with diabetes mellitus.

Study	Patient characteristics	Treatments	Follow-up (years)	Baseline BP (mmHg)	BP difference vs control (mmHg)	Total deaths (approximate rate)[a]
Monotherapy vs placebo						
IDNT ($n=1715$) (55)	Type 2 DM + nephropathy	Irbesartan ($n=579$); placebo ($n=569$); amlodipine ($n=567$)	2.6	159/87	− 3.3	263 (55)
RENAAL ($n=1513$) (56)	Type 2 DM + nephropathy	Losartan ($n=751$); placebo ($n=762$)	3.4	153/82	− 2	313 (60)
IRMA 2 ($n=590$) (57)	Type 2 DM + persistent microalbuminuria	Irbesartan 150 mg ($n=195$); irbesartan 300 mg ($n=195$); placebo ($n=201$)	2.0	153/90	− 3	4 (2.5)
TRANSCEND ($n=5927$) (58)	Cardiovascular disease or DM with end-organ damage	Telmisartan ($n=2954$); placebo ($n=2972$)	4.7	141/82	− 4	713 (25)
DIRECT-Renal ($n=5231$) (59)	Type 1 and type 2 DM, normoalbuminuria	Candesartan ($n=2613$); placebo ($n=2618$)	4.7	118/73	− 3.3	99 (4)
ROADMAP ($n=4\,447$) (60)	Type 2 DM, normoalbuminuria + ≥ 1 cardiovascular risk factor	Olmesartan ($n=2232$); placebo ($n=2215$)	3.2	136/81	− 3.0;	41 (2.1);
Combination therapy						
ONTARGET ($n=25\,620$) (61)	Cardiovascular disease or DM with end-organ damage	Ramipril ($n=8576$); telmisartan ($n=8542$); ramipril + telmisartan ($n=8502$)	4.7	142/82	− 2.4; (combination vs ramipril)	3068 (25); (all groups)
ADVANCE ($n=11\,140$) (62)	Type 2 DM + cardiovascular disease or ≥ 1 risk factor	Perindopril + indapamide (N = 5569); Placebo ($n=5571$)	4.3	145/81	− 5.6	879 (18)
ACCOMPLISH ($n=11\,506$) (63)	Hypertension + cardiovascular disease or DM (in 60% of patients)	Benazepril + amlodipine ($n=5744$); Benazepril + hydrochlorothiazide; ($n=5762$)	3.0	145/80	− 1.1; (Ben + Am vs; Ben + Hyd)	498 (14); (both groups)
Comparison of blood pressure targets						
ACCORD BP ($n=4733$) (64)	Type 2 DM at high risk for cardiovascular events	Target BP < 120 mmHg systolic ($n=2362$); target BP < 140 mmHg systolic ($n=2371$);	5.0; (for mortality)	139/76	− 14.2	249 (10)

[a] Approximate rate given for placebo group unless stated, expressed as deaths per 1000 patient-years. Am: amlodipine; Ben: benazepril; BP: blood pressure (systolic if available); DM: diabetes mellitus; Hyd: hydrochlorothiazide.

Trial names: IDNT, Irbesartan Diabetic Nephropathy Trial; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study; IRMA 2, Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study; TRANSCEND, Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease; DIRECT, Diabetic Retinopathy Candesartan Trials; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention study; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; ADVANCE, Action in Diabetes and Vascular Disease, Preterax and Diamicron-MR Controlled Evaluation Trial; ACCOMPLISH, Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension; ACCORD BP, Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial.

Table II. Summary of results of large randomized trials with renal endpoints including patients with diabetes mellitus.

	Albuminuria		Renal endpoints			Cardiovascular		Mortality	
Study	New-onset	Progression	Primary endpoint or renal events	Doubling of serum creatinine	ESRD or dialysis	All events	Stroke	All-cause	Cardiovascular
Monotherapy vs placebo									
IDNT (55)									
Irbesartan vs placebo	–	–	−20% ($P=0.02$)	−33% ($P=0.003$)	−23% (NS)	−10% (NS)	+1% (NS)	−8% (NS)	+8% (NS)
Amlodipine vs placebo	–	–	+4% (NS)	+6% (NS)	0% (NS)	0% (NS)	−35% (NS)	−12% (NS)	−21% (NS)
RENAAL: Losartan vs placebo (56)	–	−35% in UACR ($P=0.001$)	−16% ($P=0.02$)	−25% ($P=0.006$)	−28% ($P=0.002$)	−10% (NS)	–	+2% (NS)	–
IRMA 2: Irbesartan 300 mg vs placebo (57)	–	−38% in urine albumin ($P<0.001$)	−70% ($P<0.001$)	–	–	–	–	Irbesartan: 8; placebo: 5	–
TRANSCEND: Telmisartan vs placebo (58)	-	−42% ($P=0.018$)	+10% (NS)	+59% ($P=0.031$)	−29% (NS)	−8% (NS)	−17% (NS)	+5% (NS)	+3% (NS)
DIRECT-Renal: Candesartan vs placebo (59)	−5% (NS) (primary renal endpoint)	–	Also a −5.5% change in UAER ($P=0.024$)	–	–	–	–	Candesartan: 51; placebo: 48	–
ROADMAP: Olmesartan vs placebo (60)	23% delay in time to onset ($P=0.01$) (primary endpoint)	–	–	0% (NS) (23 patients in each group)	Not observed in any patients	0% (NS)	–	+70% (NS)	+394% ($P=0.01$) (olmesartan: 15; placebo: 3)
Combination therapy									
ONTARGET (61)									
Telemisartan vs ramipril	−6% (NS)	−17% (NS)	0% (NS)	+11% (NS)	+7% (NS)	+1% (NS)	−9% (NS)	−2% (NS)	0% (NS)
Combination vs ramipril	−12% ($P=0.003$)	−24% ($P=0.019$)	+9% ($P=0.037$)	+20% (NS)	+33% (NS)	−1% (NS)	−7% (NS)	+7% (NS)	+4% (NS)
ADVANCE: Perindopril + indapamide vs placebo (62)	−21% ($P=0.0001$)	−22% ($P=0.001$)	−21% ($P<0.0001$)	+21% (NS)	+18% (NS)	−14% ($P=0.020$)	−6% (NS)	−14% ($P=0.025$)	−18% ($P=0.027$)
ACCOMPLISH: Benazepril + amlodipine vs benazepril + hydrochlorothiazide (63)	–	–	−48% ($P<0.0001$)	−49% ($P<0.0001$)	−47% (NS)	−17% ($P=0.002$)	−16% (NS)	−10% (NS)	−20% (NS)
Comparison of blood pressure targets									
ACCORD BP: Target < 120 mmHg vs target, < 140 mmHg systolic (64)	30.2% vs 32.3% (NS)	6.6% vs 8.7% ($P=0.009$)	–	24% vs 16% ($P<0.001$) (elevated serum creatinine only)	No significant difference	−13% (NS) (non-fatal MI only)	−41% ($P=0.01$)	+7% (NS)	+6% (NS)

MI, myocardial infarction; NS, not significant; UACR, urinary albumin-to-creatinine ratio; UAER, urinary albumin excretion rate. Full names of studies given in Table I.

groups developed microalbuminuria in each of the three studies, with a hazard ratio (candesartan vs placebo) of 0.95 in the combined analysis ($P = 0.60$). The annual rate of change in urinary albumin excretion rate was 5.5% lower with candesartan ($P = 0.024$); this corresponds to an absolute reduction of 0.11 μg/min, which the authors describe as modest and of uncertain clinical significance. However, it must be remembered that the study was not powered for a renal endpoint. The number of deaths was similar in the candesartan (51 deaths) and placebo (48 deaths) groups.

The most recent study in this category is the ROADMAP trial (60), in which olmesartan was compared with placebo in a group of 4447 normoalbuminuric patients with type 2 diabetes. The primary endpoint was new-onset microalbuminuria. Olmesartan delayed the time to onset of microalbuminuria by 23% ($P = 0.01$), and the number needed to treat for 5 years to prevent one case of new-onset microalbuminuria was 41 patients. Secondary end-points included cardiovascular events and all-cause and cardiovascular mortality. The total number of cardiovascular events was low and was the same with both treatments. However, there were 15 cases of death from cardiovascular causes in the olmesartan group compared with three cases in the placebo group ($P = 0.01$). The difference was attributable in part to a higher rate of cardiovascular death with olmesartan in patients with established coronary artery disease, especially those in the lowest quartile of systolic blood pressure on treatment and those with the largest reductions in blood pressure with treatment. The study authors concluded that these findings could be consistent with the "J-curve effect", but that a direct effect of olmesartan could not be ruled out.

The studies considered in this section suggest that treatment with ARBs can delay the onset of microalbuminuria and progression to macroalbuminuria, and reduce the incidence of manifestations of more severe renal disease such as doubling of serum creatinine and need for dialysis, although there were inconsistencies between different renal endpoints. However, none of the trials showed a significant benefit of ARBs on mortality. The lack of significant effect might be expected in trials with relatively small numbers of deaths, such as IRMA 2 and DIRECT. However, it is of more concern in those trials, which, because of their large size and/or the high-risk nature of their patients, involved substantial numbers of deaths, or, as in ROADMAP, showed an increased rate of cardiovascular death with ARB treatment. A recent analysis (69) of 16 randomized trials in predominantly hypertensive patients since 2000 indicated that only three trials (ASCOT-BPLA (70), ADVANCE (62) and HYVET (71)) showed a significant reduction in all-cause mortality. The successful treatments in these three studies were amlodipine (± perindopril), perindopril + indapamide, and indapamide (± perindopril), respectively. The other 13 studies, individually and when pooled, showed no significant mortality benefit (odds ratio 0.996 for the pooled analysis).

Specific combinations

Many hypertensive patients in clinical practice receive more than one antihypertensive drug, and the use of combination therapy is widely recommended in hypertension guidelines. Combinations may be especially important for patients with diabetes, for whom recommended blood pressure targets are challenging. It should be pointed out that in most large recent hypertension trials, the study drug is given on top of usual antihypertensive therapy, which is often left to the discretion of the investigator. Thus, most trials evaluate the efficacy of combinations of drugs, but the type and dose of the components other than the randomized study drug are not standardized. However, three large recent trials have explicitly studied specific combinations, with striking results.

In the very large ONTARGET trial (61,72), telmisartan and the combination of telmisartan and ramipril were compared with ramipril alone in patients with cardiovascular disease or diabetes with end-organ damage. There were no significant differences between the telmisartan and ramipril groups for any renal, cardiovascular or mortality endpoint (Table II). However, the comparison between the combination and ramipril alone revealed important differences.

The combination was more effective than ramipril alone in preventing new-onset microalbuminuria and progression of pre-existing microalbuminuria, with hazard ratios of 0.88 ($P = 0.003$) and 0.76 ($P = 0.019$), respectively. On the other hand, the primary renal endpoint, the composite of doubling of serum creatinine, dialysis or death, occurred significantly more frequently with the combination than with ramipril (hazard ratio 1.09, $P = 0.037$); each component was numerically more frequent with the combination, by 20%, 33% and 7%, respectively. Declines in estimated glomerular filtration rate were greater with the combination than with ramipril ($P < 0.0001$). Rates of cardiovascular endpoints and mortality were similar in the combination and ramipril groups. Renal abnormalities were reported as adverse events in significantly more patients in the combination group than with ramipril (relative risk 1.33, $P < 0.0001$), and more patients stopped medication because of renal abnormalities with the combination than with ramipril (relative risk 1.58, $P < 0.005$). Thus, the addition of telmisartan to ramipril reduced the incidence of proteinuria, but caused a more rapid decline in glomerular filtration rate, increased the incidence of major renal events, and showed no benefit in terms of cardiovascular events or mortality. This may be

one of the reasons why guidelines do not recommend this combination.

The ADVANCE trial is the largest trial performed in diabetics, involving 11 140 patients. It compared a fixed-dose combination of perindopril and the original diuretic indapamide with placebo in patients with type 2 diabetes and a history of major cardiovascular disease or at least one other cardiovascular risk factor (62,73). Combination therapy reduced the composite renal endpoint (new-onset microalbuminuria, new-onset nephropathy, doubling of serum creatinine or end-stage renal disease) by 21% (hazard ratio 0.79, $P < 0.0001$). There were also significant reductions in new-onset microalbuminuria (21%) and progression from microalbuminuria to macroalbuminuria (31%). The number needed to treat for 5 years to prevent one case of new-onset microalbuminuria in ADVANCE was 16 patients, which may be contrasted with the corresponding figure of 41 patients with ARB treatment in the ROADMAP trial (60). Later-stage renal events were infrequent in the ADVANCE population, and end-stage renal disease occurred with similar frequency in the combination and placebo groups. However, new or worsening nephropathy was reduced in patients with an UACR ≥ 30 (74). In contrast to the trials of ARBs described in the previous section, the renal benefits of the perindopril + indapamide combination were accompanied by significant reductions in all-cause mortality (by 14%, $P = 0.025$), cardiovascular death (by 18%, $P = 0.027$) and coronary events (by 14%, $P = 0.020$). At least three further features of the ADVANCE trial are notable. Firstly, almost all other antihypertensive treatments were allowed (including RAAS-inhibitors in 73% of patients of the control group, a first in these trials), except that thiazide diuretics were not permitted. The effectiveness of the permitted treatments was illustrated by the fact that regression of albuminuria by at least one stage was observed in 50.2% of patients in the placebo group; nonetheless, active treatment provided a further benefit of 16% in the incidence of regression ($P = 0.0017$). Secondly, significant reductions in renal events were seen in all subgroups of patients defined by baseline blood pressure, including those with starting blood pressure below 125/75 mmHg. Indeed, the lowest risk for renal events was observed in patients with achieved blood pressure levels below 110 mmHg systolic or 65 mmHg diastolic. Thirdly, a recent analysis has shown that the relative risk of all-cause mortality was reduced to a similar extent in patients with or without nephropathy, and whatever their CKD stage at baseline (74). One issue not resolved by ADVANCE was whether the observed benefits were independent of blood pressure reduction, because the blood pressure achieved was lower in the active treatment group by an average of 5.6 mmHg systolic and 2.2 mmHg diastolic. However, since the majority of diabetic patients with hypertension in clinical practice do not reach their target blood pressure (75), the greater antihypertensive efficacy of the perindopril + indapamide combination could be regarded as an additional positive result.

The third trial in this group is ACCOMPLISH (63,76), which compared two fixed-dose combinations – benazepril + amlodipine and benazepril + hydrochlorothiazide – in 11 506 patients with hypertension and a history of cardiovascular disease or diabetes; approximately 60% (6946) of randomized patients had diabetes. The primary endpoint was the composite of cardiovascular events and cardiovascular death, and the trial was halted prematurely because of a significant reduction in this endpoint in the benazepril + amlodipine group (hazard ratio 0.80, $P < 0.001$). There was a significant reduction in the composite of all cardiovascular events (17%, $P = 0.002$), but the reductions in all-cause death (10%), cardiovascular death (20%) and stroke (16%) did not reach significance. The primary renal endpoint, the composite of doubling of serum creatinine and end-stage renal disease, was almost halved in the benazepril + amlodipine group (hazard ratio 0.52, $P < 0.0001$), related mainly to a 49% reduction in doubling of serum creatinine ($P < 0.0001$). As in the ADVANCE trial, dialysis was infrequent, occurring in seven patients in the benazepril + amlodipine group and 13 patients in the benazepril + hydrochlorothiazide group (NS). Despite the marked reduction in later-stage renal events with benazepril + amlodipine, the proportion of patients with baseline microalbuminuria who regressed to normoalbuminuria was substantially lower in this group (41.7%) than with benazepril + hydrochlorothiazide (68.3%, $P = 0.0016$). The systolic blood pressure level in the two treatment groups differed by less than 1 mmHg. In the diabetic subgroup (77), the incidence of the primary endpoint was also significantly lower in the benazapil + amlodipine group with a hazard ratio of 0.79, similar to that in non-diabetic patients (hazard ratio 0.82). The renal outcome results from the ACCOMPLISH study confirm the need for future hypertension trials to consider cardiovascular and renal outcomes jointly (76), and indicate that the mechanisms that facilitate the progression of cardiovascular disease have similarities to those that lead to the progression of renal disease.

Intensive therapy – more is not always better

The final trial that we consider was of very different design. The recent ACCORD study (64) in 4733 patients with type 2 diabetes did not compare specific drugs or combinations, but rather evaluated the benefit of intensive blood pressure lowering to a target of < 120 mmHg systolic compared with standard therapy with a target of < 140 mmHg. In this trial, the drug regimens used in both groups were at the discretion of the individual investigators, and

treatments were administered in open-label fashion. Essentially, drugs from all the major antihypertensive drug classes were used more frequently in the intensive treatment group (Figure 2). The mean numbers of antihypertensive drugs taken at 1 year was 3.4 in the intensive group and 2.1 in the standard therapy group, and by the end of the study 41% of patients in the intensive group were taking drugs from ≥ 4 classes (including RAAS inhibitors). Achieved blood pressures averaged 119/64 in the intensive group and 134/71 with standard therapy. There was a significant reduction in the occurrence of macroalbuminuria in the intensive group (6.6% vs 8.7%, $P = 0.009$), but elevated serum creatinine was reported more frequently with intensive (23.8%) compared with standard therapy (15.5%, $P < 0.001$). There was no benefit of intensive therapy in the primary endpoint (the composite of myocardial infarction, stroke or cardiovascular death), or in all-cause and cardiovascular mortality, or in the frequency of end-stage renal disease or the need for dialysis. On the other hand, there was a marked reduction in the frequency of stroke with intensive therapy (hazard ratio 0.59, $P = 0.01$). A further consideration is that the rate of serious adverse events was significantly higher with intensive therapy. Although there was variation between different endpoints, intensive therapy showed little evidence of benefit, and some signals of possible harm.

At least four points emerge with some clarity from this disparate group of studies of combination therapy and blood pressure targets. Firstly, the effects of treatment can vary widely among different endpoints. Secondly, combinations of antihypertensive drugs vary widely in their ability to prevent major renal and cardiovascular events, even if they produce similar reductions in blood pressure. Thirdly, the addition of further antihypertensive drugs in patients already taking one or more antihypertensive drugs may not improve renal and mortality outcomes, even if it produces a further reduction in blood pressure. Intensive blood pressure lowering to < 120 mmHg systolic using 'ad hoc' combinations and doses in the ACCORD trial did not reduce major renal events or mortality compared with standard therapy. Finally, the only treatment providing primary and secondary prevention of renal events together with significant benefits in terms of all-cause and cardiovascular mortality, relative to a control group including RAAS inhibitors, was the perindopril + indapamide combination in the ADVANCE study. This trial can be considered as the study that fits best with the current reappraisal of the ESH guidelines with regard to the achievement of BP objectives, use of an adequate combination and achieving simultaneous protection of the kidney and the cardiovascular system (78).

Conclusions

Overall, the results of the trials reviewed here support the concept that aggressive blood pressure lowering is a vital element in the management of patients with type 2 diabetes, especially if they have evidence of renal involvement. However, it is clear that antihypertensive drugs and combinations differ widely in their effects, particularly regarding their capacity to reduce mortality, and the differences may be especially important in diabetic patients. Agents such as beta-blockers and thiazide diuretics may have adverse metabolic effects and may not be ideal choices in patients with, or at high risk of developing, diabetes. The near-universal use of more than one drug class to achieve target blood pressure in diabetic patients has important implications for clinical trial design and interpretation. Beneficial and adverse effects of one drug may be accentuated or minimized by concomitant therapies, but the types and doses of background therapies are often not standardized in trials. Explicit evaluation of fixed-dose combinations is in its infancy, but has

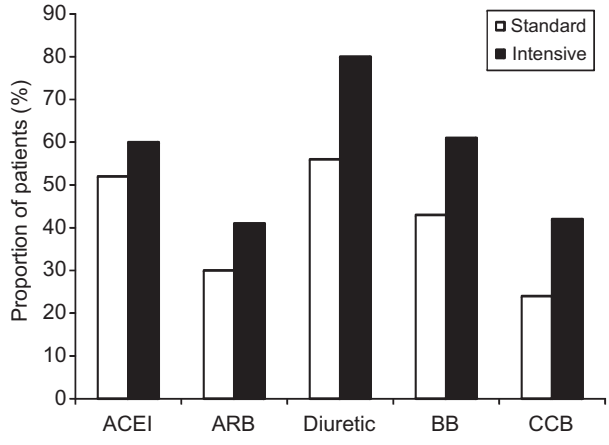

Figure 2. Main classes of antihypertensive drugs prescribed at the last study visit in patients in the intensive and standard treatment groups in the ACCORD trial. Alpha blockers, reserpine and other antihypertensive were also prescribed in $< 25\%$ of patients in either group. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; BB, beta-blocker; CCB, calcium channel blocker. Data from Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial (ACCORD) Study Group (64).

already highlighted large differences in their effect on outcome, even when their effect on blood pressure is the same. Finally, the strategy of simply adding additional drugs to patients already receiving two or more in an effort to drive blood pressure to ever lower levels may be counterproductive.

A lack of concordance among different renal endpoints and between renal and mortality endpoints emerged clearly from this review, and is consistent with concerns expressed over the use of proteinuria as a surrogate for kidney disease progression (79,80). Rates of end-stage renal disease or dialysis may also be of limited value, since these outcomes are relatively infrequent, and patients with macroalbuminuria are more likely to die than to progress to renal failure (48). Ultimately, all-cause and cardiovascular mortality are the most reliable trial endpoints, and so far only few and limited subgroups of trials have demonstrated simultaneous reduction of microalbuminuria and mortality in diabetic patients.

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Research Article

Validation of a therapeutic scheme for the treatment of resistant hypertension

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Abstract

We tested the hypothesis that a therapeutic strategy of substituting the diuretic (most commonly hydrochlorothiazide) with chlorthalidone (50 mg/day), and, if needed, the calcium channel blocker with the highest dose of the most commonly used calcium antagonist (amlodipine 10 mg), and adding on top a direct renin inhibitor (aliskiren 300 mg) is effective to treat resistant hypertensive patients not responding to spironolactone. The scheme was tested in a group of 76 patients who had true treatment resistant hypertension (24-hour mean blood pressure ≥130/80 mm Hg while receiving three or more drugs). An effective response to spironolactone was defined as 24-hour ambulatory systolic blood pressure (SBP) drop by more than 20 mm Hg, and was obtained with 25–50 mg in 60 patients (78.9%). In patients with inadequate response to spironolactone (n = 16), we administered the triple combination plus the remaining therapy, a mean decrease of 29 mm Hg (95% CI 11–48; $P = .004$) for SBP and 12 mm Hg (95% CI: 4–20 mm Hg) for diastolic BP were observed. In only 1 of 16 patients (6%), the response was considered as insufficient. These data indicate the need for further testing this scheme that looks really promising to treat resistant hypertensive patients not responding to spironolactone. J Am Soc Hypertens 2011;■(■):1–7.

Keywords: resistant hypertension; blood pressure control; ambulatory blood pressure measurement; spironolactone; direct renin inhibition.

Introduction

Resistant hypertension (RH) is defined as blood pressure (BP) that remains above goal (>140/90 mm Hg) in spite of the concurrent use of three or more antihypertensive agents, one of them being a diuretic and all prescribed at optimal doses.[1] Although the exact prevalence is unknown, several studies indicate that RH is a common clinical problem,[2] and it is clearly associated with poor cardiovascular prognosis.[3] Recent data from our group[4] using ambulatory blood pressure monitoring (ABPM) indicate that 12% of treated hypertensive patients can be classified as being resistant.

Treatment of RH is focused on identification and reversal of lifestyle factors contributing to treatment resistance, in particular high salt intake, accurate diagnosis and appropriate treatment of secondary causes of hypertension, and use of effective multidrug regimens.[1] Recommendations for the pharmacological treatment remain largely empiric because of the lack of systematic assessments of three or four drug combinations. Moreover, therapeutic studies of RH are limited by the high cardiovascular risk of these patients, which generally precludes safe withdrawal of medications.[1] Specific pharmacological recommendations include the use of long-acting diuretics, mineralocorticoid receptor antagonists,[5–7] or endothelin-receptor antagonists.[8] Among these pharmacological options, spironolactone has demonstrated to be a useful tool for BP control in true

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RH patients, but there are no clear recommendations for those patients who do not respond to spironolactone.[5]

We have tested the hypothesis that a triple combination consisting of the substitution of the diuretic (hydrochlorothiazide 50 mg/day or furosemide 40–80 mg/day) with chlorthalidone (50 mg/day), and, if needed, that of the calcium channel blocker (CCB) with the highest dose of the most commonly used calcium antagonist amlodipine to 10 mg, keeping equal the rest of the treatment (angiotensin-converting enzyme [ACEI] or angiotensin receptor blocker [ARB], alpha- or beta-blocker) and adding on top a direct renin inhibitor (aliskiren 300 mg) could be effective to treat patients not responding to spironolactone.

Methods

Study Design

We conducted a prospective study intended to evaluate the response to aldosterone blockade in patients with true RH, and to analyze the effects of a direct renin inhibitor, aliskiren, in combination with 50 mg of chlorthalidone and 10 mg of amlodipine plus the other nondiuretic, non-CCB medications, in those RH patients who did not respond to spironolactone. We enrolled consecutively patients arriving in our unit if they fulfilled the following entry criteria: age between 18 and 75 years, BP levels with mean values on an 24-hour ABPM >130/80 mm Hg while receiving three or more drugs, one being a diuretic, at adequate doses, estimated glomerular filtration rate (eGFR) >40 mL/min/1.73 m^2, serum potassium levels <4.8 mEq/L, and previous history of spironolactone intolerance. Blood and urine samples were obtained to measure serum creatinine for the eGFR, serum glucose, total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides, as well as serum uric acid, sodium, and potassium. Urinary albumin-to-creatinine ratio was averaged from three morning void urine samples. A 24-hour ABPM was performed at baseline to confirm that patients had true resistant hypertension. This study was approved by our local ethic committee, and all subjects gave informed consent.

Seventy-six patients fulfilled the entry criteria (recruitment period between September 2009 and September 2010) and were treated initially with spironolactone 25–50 mg/day (25 mg/day for those patients with eGFR between 40–60 mL/min/1.73 m^2, 50 mg/day for those with eGFR >60 mL/min/1.73m^2), added on top of former antihypertensive treatment. After 2 months, casual BP measurements and ABPM were repeated and a blood sample was obtained to measure serum creatinine and potassium. Response to spironolactone was defined to be effective if 24-hour ambulatory systolic BP dropped ≥20 mm Hg. In nonresponders, spironolactone was withdrawn and the pharmacologic scheme including aliskiren 300 mg/day, accompanied by the previously mentioned changes in diuretic (chlorthalidone 50 mg) and CCB (amlodipine 10 mg) therapy with the rest of the treatment remaining unchanged was started.

BP Measurements

BP was measured at the office with a validated semiautomatic oscillometric device, after 5-minute rest in a sitting position. BP values were estimated as the mean of three readings. Thereafter, 24-hour ABPM was performed using SpaceLabs 90207 (SpaceLabs Inc.; Redmond, WA, USA) automated noninvasive oscillometric device, programmed to register BP at 20-minute intervals for the daytime period and at 30-minute intervals for the nighttime period. The majority of measurements were performed on working days, and the patients were instructed to maintain their usual activities, return the following morning for device removal, and keep the arm extended and immobile at the time of each cuff inflation. Daytime and nighttime periods were defined individually according to the patient self-reported data of going-to-bed and getting-up times. Both office and ABPM were repeated 2 months after starting spironolactone. In those nonresponding, the same methodology was performed again after 2 and after 4 months of treatment with the triple combination and our therapeutic rescue scheme (see the previous section).

Statistical Analysis

Data are presented as frequencies and percentages for qualitative variables and as mean ± standard deviation (or median [interquartile range]) for quantitative variables. Differences in study variables between groups were assessed with the Pearson χ^2 for qualitative variables and the Student's *t* test (or Mann-Whitney test) for quantitative data. All tests were two-tailed and a P value < .05 was considered statistically significant. The SPSS for Windows version 15.0 software (SPSS Inc., Chicago, IL) was used for statistical analysis.

Results

Pharmacological Approach

Our study population composed 76 patients: their mean age was 65.3 ± 9.6 years; 52.6% were female and 42.1% had diabetes. Table 1 summarizes the baseline characteristics of these patients. Figure 1 shows office and ambulatory systolic BP (SBP) and diastolic BP (DBP) before and during spironolactone administration. The mean decrease in office SBP and DBP was 21 mm Hg (95% CI: 15–27 mm Hg) and 7 mm Hg (95% CI: 4–10 mm Hg), respectively (P < .001). Ambulatory 24-hour SBP and DBP decreased a mean of 23 mm Hg (95% CI: 18–27 mm Hg) and 9 mm Hg (95% CI: 7–11 mm Hg), respectively (P < .001).

Table 1
Baseline characteristics of true RH patients treated with spironolactone

Characteristics	Value
n	76
Age, y	65.3 ± 9.6
Gender, % female	52.6
Waist circumference, cm	106 ± 12
BMI, kg/m^2	31.2 ± 5.3
Duration of hypertension, y	20.2 ± 11.0
Smokers, %	9.2
Diabetics, %	42.1
Duration of diabetes, y	8.9 ± 6.4
Previous CV disease, %	23.7
Creatinine, mg/dL	0.92 ± 0.25
Total cholesterol, mg/dL	190.7 ± 34.9
HDL cholesterol, mg/dL	54.7 ± 13.8
LDL cholesterol, mg/dL	108,1 ± 32,5
Triglycerides, mg/dL	152.7 ± 125.9
UAE, mg/g	17.5 [6.4–78.7]
UAE >30 mg/g, %	39.3
LVH by ECG, %	27.6
eGFR by MDRD, mL/min/1.73 m^2	80.4 ± 19.7
PWV, m/s	11.2 ± 4.0
SBP, mm Hg	
Office	157 ± 19
Home	160 ± 16
24 hours	147 ± 13
Daytime	149 ± 13
Nighttime	141 ± 17
Central	143 ± 17
DBP, mm Hg	
Office	85 ± 12
Home	86 ± 10
24 hours	78 ± 10
Daytime	80 ± 10
Nighttime	74 ± 11
Central	85 ± 13
Mean number of antihypertensive drugs	3.8 ± 0.7
Diuretics, %	100
ACE inhibitors/ARBs, %	100
Calcium channel blockers, %	69.7
Beta-blockers, %	47.4
Alpha-blockers, %	46.1
Direct vasodilators, %	9.2
Concomitant therapies	
Oral antidiabetics, %	32.9
Insulin, %	5.3
Statins, %	65.8
Fibrates, %	7.9
Antiplatelet agents, %	26.3

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CV, cardiovascular; DBP, diastolic blood pressure; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; MDRD, Modification Diet Renal Disease study; PWV, pulse wave velocity; RH, resistant hypertension; SBP, systolic blood pressure; UAE, urinary albumin excretion.

Analyses of daytime and nighttime BP showed comparable BP reductions.

Response to spironolactone rate was effective in 78.9% (n = 60). Nonresponders to spironolactone (n = 16) were younger and had higher values of office and ambulatory BP at baseline than responders, without differences in other clinical and biochemical characteristics between the two groups (Table 2). Table 3 shows office and ambulatory BP values before and after 2 months of treatment with spironolactone in responders and nonresponders. In nonresponders, spironolactone was withdrawn and aliskiren 300 mg/day was administered combined with amlodipine 10 mg/day and chlorthalidone 50 mg/day, leaving the rest of the treatment unchanged. Two months later, nonresponders to spironolactone showed a mean decrease in clinic SBP and DBP of 29 mm Hg (95% CI: 11–48 mm Hg, P = .004) and 12 mm Hg (95% CI: 4–20 mm Hg, P = .005), respectively. Decreases in 24-hour, daytime, and

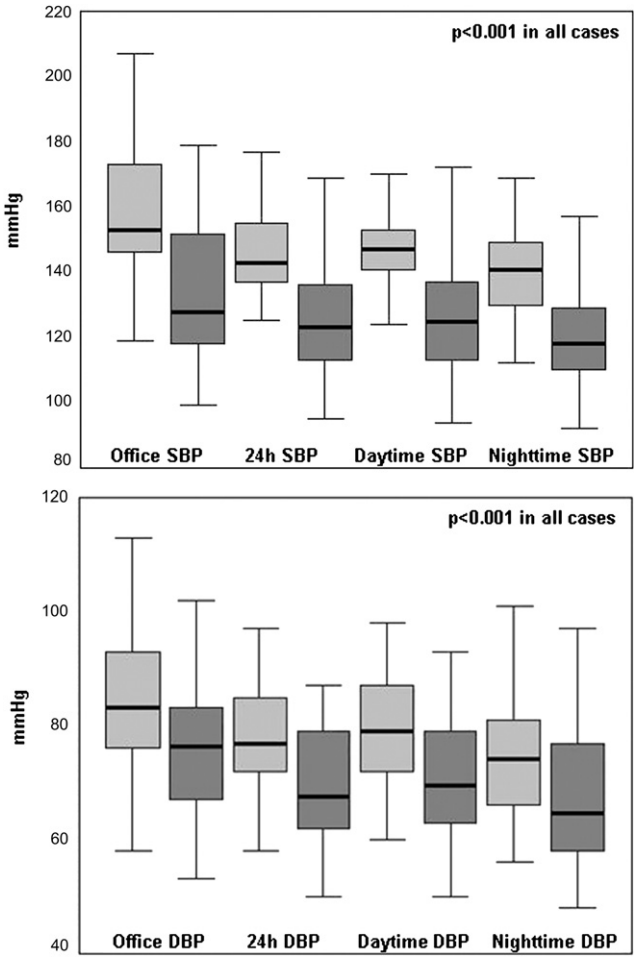

Figure 1. Box-plot graphic representation of office and ambulatory systolic (top) and diastolic (bottom) blood pressure before (clear box) and during (dark box) spironolactone administration. P values refer to paired t test comparisons of blood pressures before and during spironolactone use.

Table 2
Clinical and biochemical differences between responders and non responders to spironolactone

Characteristics	Responders	Non responders	*P*
n	60	16	
Age, y	66.5 ± 9.4	60.5 ± 9.1	.025
Gender, % female	58.3	31.3	.054
Waist circumference, cm	106 ± 13	107 ± 11	.810
BMI, kg/m^2	31.3 ± 5.6	30.5 ± 4.0	.576
Duration of hypertension, y	20.9 ± 11.1	17.7 ± 10.1	.309
Smokers, %	8.3	12.5	.174
Diabetics, %	41.7	43.8	.881
Duration of diabetes, y	9.3 ± 6.5	7.5 ± 6.5	.542
Previous CV disease, %	25.0	18.8	.601
Creatinine, mg/dL	0.91 ± 0.27	0.96 ± 0.20	.477
Serum potassium, mEq/L	4.27 ± 0.50	4.22 ± 0.30	.750
Total cholesterol, mg/dL	189.1 ± 35.3	196.4 ± 33.5	.466
HDL cholesterol, mg/dL	55.1 ± 12.8	53.3 ± 17.5	.651
LDL cholesterol, mg/dL	107.2 ± 33.4	111.5 ± 29.3	.649
Triglycerides, mg/dL	148.4 ± 114.0	168.9 ± 167.0	.566
UAE, mg/g	12.9 (5.4–80.4)	30.5 (9.0–68.6)	.433
UAE > 30 mg/g, %	36.2	50.0	.352
LVH by ECG, %	23.3	43.8	.247
eGFR by MDRD, mL/min/1.73 m^2	80.4 ± 20.9	80.6 ± 15.4	.968
PWV, m/s	11.6 ± 3.8	9.9 ± 4.9	.156
SBP, mm Hg			
Office	154 ± 17	169 ± 24	.004
Home	159 ± 15	166 ± 18	.092
24 hours	146 ± 13	148 ± 15	.657
Daytime	148 ± 13	150 ± 12	.592
Nighttime	141 ± 15	142 ± 23	.841
Central	140 ± 15	152 ± 21	.009
DBP, mm Hg			
Office	83 ± 12	92 ± 13	.007
Home	85 ± 10	89 ± 11	.177
24 hours	77 ± 10	81 ± 11	.160
Daytime	79 ± 10	84 ± 11	.106
Nighttime	74 ± 10	76 ± 12	.468
Central	83 ± 13	91 ± 15	.046
Mean number of antihypertensive drugs	3.8 ± 0.8	3.7 ± 0.6	.905

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CV, cardiovascular; DBP, diastolic blood pressure; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; MDRD, Modification Diet Renal Disease study; PWV, pulse wave velocity; RH, resistant hypertension; SBP, systolic blood pressure; UAE, urinary albumin excretion.

nighttime ambulatory BP were also observed (Table 3, Figure 2). Only one patient (6%) exhibited an inadequate response to treatment. In those who responded, the dose of chlorthalidone was downtitrated to 25 mg/day and a second measurement of BP was done 2 months later. Only in two patients (13.3%), the dose was raised again because BP increased more than 5 mm Hg.

Safety and Tolerability

During spironolactone treatment, serum creatinine increased on average from 0.92 ± 0.25 mg/dL to 1.00 ± 0.29 mg/dL ($P < .001$ for the difference), serum potassium from 4.26 ± 0.45 mEq/L to 4.64 ± 0.50 mEq/L ($P < .001$ for the difference), and sodium decreased from 142.4 ± 3.3 mEq/L to 141.5 ± 3.0 mEq/L ($P = .031$ for the difference). A total of 12 (15.8%) patients suffered collateral effects: gynecomastia (n = 6), erectile dysfunction (n = 2), hyperkaliemia >6.0 mEq/L (n = 3), and 1 case of serum creatinine increased >30% from baseline.

During aliskiren treatment, no significant changes of biochemical parameters were observed in these parameters (data not shown).

Discussion

Our results confirmed the capacity of the aldosterone receptor blockers spironolactone to control BP in a high

Table 3
Changes in clinic and ambulatory BP after spironolactone (responders and nonresponders) and after aliskiren (nonresponders to spironolactone)

	Responders			Non responders				
	Pre-spironolactone	Post-spironolactone	P*	Pre-spironolactone	Post-spironolactone	P*	Post-aliskiren	P†
Clinic SBP	154 ± 17	127 ± 18	.000	169 ± 24	161 ± 16	.108	141 ± 21	.004
Clinic DBP	83 ± 12	74 ± 11	.000	92 ± 13	89 ± 15	.482	82 ± 12	.005
24-h SBP	146 ± 13	122 ± 15	.000	148 ± 15	142 ± 16	.019	135 ± 14	.011
24-h DBP	77 ± 10	69 ± 11	.000	81 ± 11	73 ± 11	.017	75 ± 10	.015
Daytime SBP	148 ± 13	123 ± 16	.000	150 ± 12	146 ± 16	.066	137 ± 16	.013
Daytime DBP	79 ± 10	70 ± 11	.000	84 ± 11	76 ± 11	.041	77 ± 11	.011
Nighttime SBP	141 ± 15	119 ± 18	.000	142 ± 23	135 ± 21	.019	130 ± 16	.009
Nighttime DBP	74 ± 10	66 ± 12	.000	76 ± 12	69 ± 14	.131	69 ± 8	.042

BP, blood pressure; DBP, diastolic BP; SBP, systolic BP.
* *P* comparison before and after spironolactone treatment.
† *P* comparison before spironolactone and after aliskiren.

percentage of patients with resistant hypertension.[6] Why are aldosterone blockers so effective? This class of drugs has demonstrated to be good antihypertensive drugs even at first step in patients with essential hypertension.[9] On the other hand, it is the treatment of choice in primary aldosteronism, together with laparoscopic adrenalectomy in the case of adenoma (10). Over the last years, compelling evidence supports the view that primary aldosteronism is more prevalent than usually considered. In fact, among consecutive newly diagnosed hypertensive patients referred to hypertension centers, its prevalence can be as high as 11.2%.[10,11] Hence, a percentage of resistant hypertension could be primary due to aldosteronism never appropriately treated with drugs blocking the effects of aldosterone. In fact, the incidence of primary aldosteronism in patients with resistant hypertension has been estimated to be even 14–23%,[12] and a rapid reversal of left ventricular hypertrophy and intracardiac volume overload have shown to take place after mineralocorticoid receptor blockade accompanied by a prominent diuretic effect.[13] Recent evidences have also shown that elevated plasma aldosterone levels directly contribute to the pathogenesis of insulin resistance and endothelial dysfunction processes that in turn contribute to maladaptive renal and cardiovascular remodeling promoting the development of resistant hypertension.[14] Thus, the concept to add spironolactone first in treatment resistant hypertension is rationale and effective as documented by our current data.

In the percentage of patients with resistant hypertension not responding to spironolactone, the increased BP is probably more dependent on vasoconstriction than on volume overload. We suggest a change in the combination therapy by adding aliskiren 300 mg combined with amlodipine 10 mg/day, chlorthalidone 50 mg/day, while maintaining ACEI, ARB, alpha- and/or beta-blocker, whatever had been previously prescribed.

The selection of amlodipine 10 mg and chlorthalidone 50 mg has been based on the excellent capacity of these drugs to control BP: amlodipine has been found to be most effective to lower BP,[15,16] to control BP variability,[17] and in association with a RAS suppressor to protect the CV and renal systems of hypertensive patients.[18,19] With respect to chlorthalidone, data indicate a higher potency to lower BP for an equal dose when compared with hydrochlorothiazide[20] that could translate into an improved renal outcome.[21] Chlorthalidone has been recognized as a valuable tool in the management of essential hypertension more effective in lowering SBP than hydrochlorothiazide, as evidenced by 24-hour ambulatory BP.[22] We considered chlorthalidone 50 mg as an adequate dose to substitute for the diuretic previously used in true resistant hypertensive patients. Nevertheless, our results support the possibility that a lower dose of chlorthalidone (25 mg/day) could be enough in more than 80% of the patients.

Aliskiren has shown to be more potent than ramipril in arterial hypertension,[23,24] than hydrochlorothiazide in obese hypertensives,[25] and also than irbesartan in patients with metabolic syndrome.[26] Aliskiren is also a useful option for the treatment of patients with stage 1 to stage 2 hypertension alone or in combination with other antihypertensives, including hydrochlorothiazide, valsartan, or amlodipine.[27] In particular, the combination of aliskiren and amlodipine has recently demonstrated in an open-label study its capacity to reduce BP, particularly in patients with stage 2 hypertension.[28] Moreover, it is possible that aliskiren plus either an ACEI or ARB may provide greater RAAS blockade than monotherapy with ACEIs or ARBs, and lead to additive improvement in BP and clinically important outcomes.[29]

Our data show that the therapeutic scheme used including aliskiren was positive with only one patient exhibiting a poor response. We believe that the role played by the other medications maintained was probably marginal since we did not change the previously prescribed medication.

To our knowledge, this is the first study intended to assess the antihypertensive efficacy of direct renin inhibition in

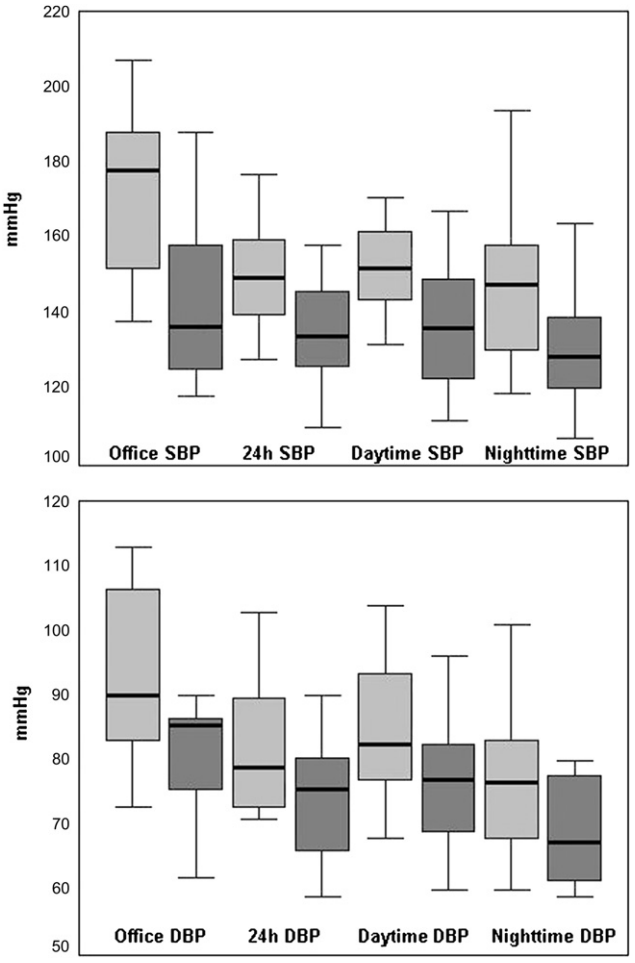

Figure 2. Box-plot graphic representation of office and ambulatory systolic (top) and diastolic (bottom) blood pressure at baseline (clear box) and during aliskiren, amlodipine, and chlorthalidone administration (dark box) in resistant hypertensive patients not responding to spironolactone.

combination with high doses of amlodipine and chlorthalidone in patients with resistant hypertension nonresponding to aldosterone receptor blockade. An incomplete inhibition of the renin angiotensin aldosterone system may be responsible for the residual organ damage and event rate in patients with hypertension, diabetes, chronic kidney disease, and heart failure treated with ACEI or ARB.[30] Both ACEI and ARB administration is accompanied by an increase in plasma renin activity that is traditionally related with increased cardiovascular risk.[31] The long-lasting direct renin inhibitor aliskiren, acting at the first and rate-limiting step of the renin angiotensin aldosterone system cascade, could prevent this reactive increase in plasma renin activity when combined with ACEIs, ARBs, or diuretics.[30] Moreover, its high specificity for human renin, together with a long half-life in plasma, comparable to that of amlodipine, and a high affinity for renal glomeruli and vasculature[32] are additional characteristics favoring the use of aliskiren in resistant hypertensive patients.

In conclusion, a high percentage of patients with resistant hypertension respond favorably to aldosterone receptor blockade with spironolactone. In those not responding, the addition of aliskiren 300 mg, combined with an adequate diuretic and high-dose amlodipine (plus the rest of therapy formerly prescribed) seems to be an adequate alternative to control hypertension in these patients.

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